CHAPTER 15

Hereditary Fundus Dystrophies

Special investigations

Electroretinography

General principles

The electroretinogram (ERG) is the record of an action potential produced by the retina when it is stimulated by light of adequate intensity. The recording is made between an active electrode embedded in a contact lens placed on the patient's cornea (or a gold foil electrode placed on the eyelid) and a reference electrode on the patient's forehead. The potential between the two electrodes is then amplified and displayed (Fig. 15.1). The ERG is elicited both in the light-adapted (photopic) and dark-adapted (scotopic) states. The normal ERG is biphasic (Fig. 15.2).

1. **The a-wave** is an initial negative deflection which arises from the photoreceptors.
2. **The b-wave** is a positive deflection, which although generated by Müller cells, represents electrical activity in the bipolar cell region. The amplitude of the b-wave is measured from the trough of the a-wave to the peak of the b-wave, and increases with both dark adaptation and increased light stimulus. The b-wave consists of b1 and b2 subcomponents. The former probably represents both rod and cone activity and the latter mainly cone activity. It is possible to single out rod and cone responses with special techniques.

Normal ERG

This consists of five recordings (Fig. 15.3). The first three are elicited after 30 minutes of dark adaptation (scotopic), and the last two after 10 minutes of adaptation to moderately bright diffuse illumination (photopic).

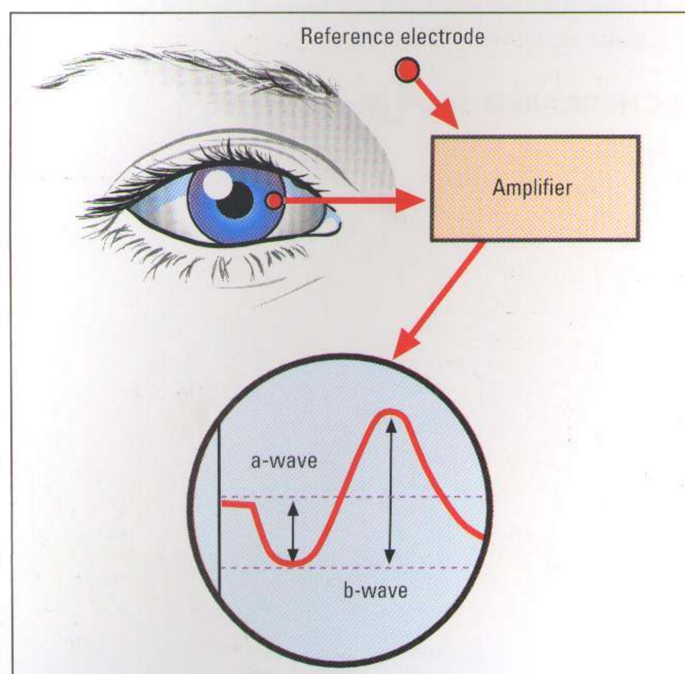


Fig. 15.1
Principles of electroretinography

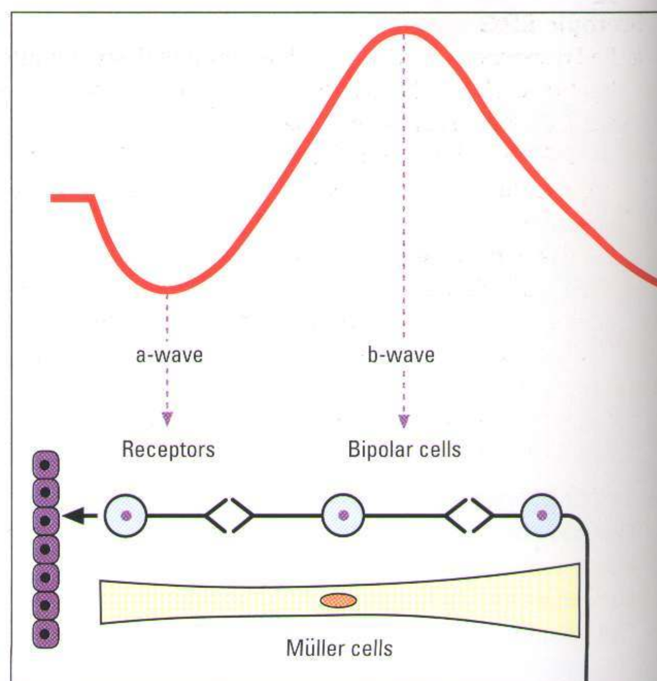


Fig. 15.2
Components and origins of the electroretinogram

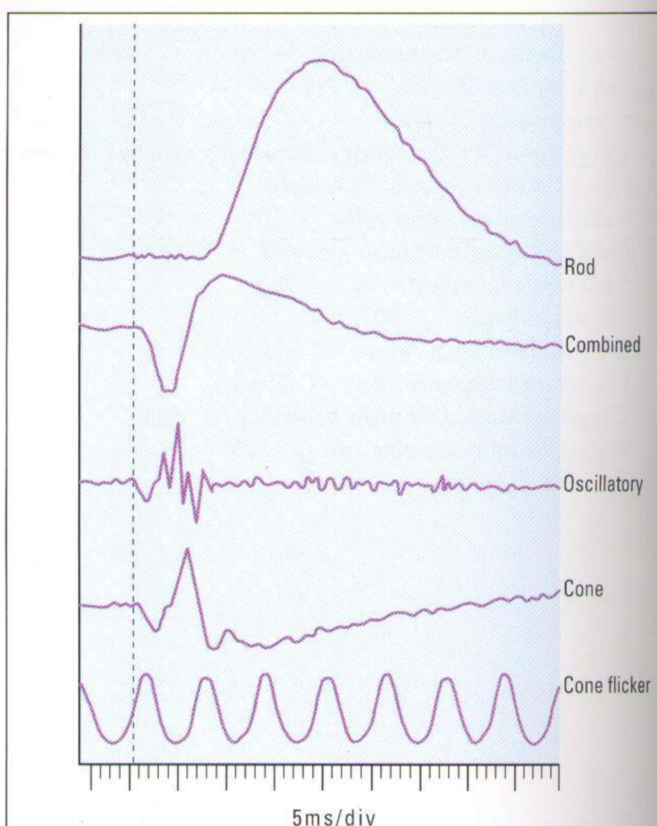


Fig. 15.3
Normal electroretinographic recordings

1. Scotopic ERG

a. Rod responses are elicited with a very dim flash of white light or a blue light, resulting in a large b-wave and a small or non-recordable a-wave.

b. Combined rod and cone responses are elicited with a very bright white flash resulting in a prominent a-wave and a b-wave.

c. Oscillatory potentials are elicited by using a bright flash and changing the recording parameters. The oscillatory wavelets occur on the ascending limb of the b-wave and are generated by cells in the inner retina.

2. Photopic ERG

a. Cone responses are elicited with a single bright flash resulting in an a-wave and a b-wave with small oscillations.

b. Cone flicker is used to isolate cones by using a flickering light stimulus at a frequency of 30 Hz to which rods cannot respond. It provides a measure of the amplitude and implicit time of the cone b-wave. Cone responses can be elicited in normal eyes up to 50 Hz, after which point individual responses are no longer recordable (critical flicker fusion).

Electro-oculography

The electro-oculogram (EOG) measures the standing potential between the electrically positive cornea and the electrically negative back of the eye (Fig. 15.4). It reflects the activity of the RPE and the photoreceptors. This means that an eye blinded by lesions proximal to the photoreceptors will have a normal EOG. In general, diffuse or widespread disease of the RPE is needed to affect the EOG response significantly. The test is performed in both light- and dark-adapted states as follows:

1. The electrodes are attached to the skin near the medial and lateral canthi.
2. The patient is asked to look rhythmically from side to side, making excursions of constant amplitude. Each time the eye moves the cornea makes the nearest electrode positive with respect to the other.
3. The potential difference between the two electrodes is amplified and recorded.

As there is much variation in EOG amplitude in normal subjects, the result is calculated by dividing the maximal height of the potential in the light (light peak) by the minimal height of the potential in the dark (dark trough). This is expressed as a ratio (Arden ratio) or as a percentage. The normal value is over 1.85 or 185%.

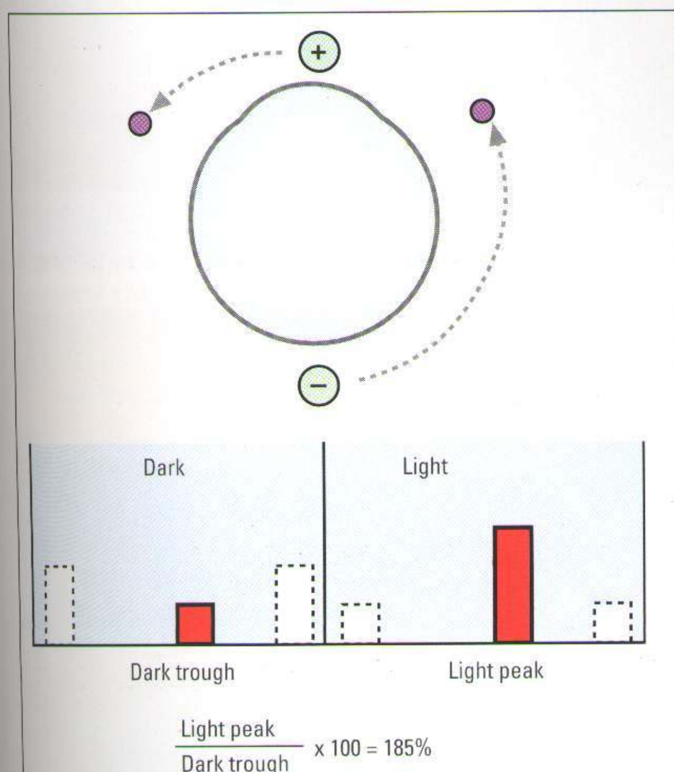


Fig. 15.4
Principles of electro-oculography

Dark adaptometry

Dark adaptation (DA) is the phenomenon by which the visual system (pupil, retina and occipital cortex) adapts to decreased illumination. Dark adaptometry is particularly useful in patients complaining of night-blindness (nyctalopia).

1. Goldmann–Weekes adaptometry is performed as follows:

a. The subject is first exposed to an intense light that will totally bleach the photoreceptors.

b. After so being rendered fully light-adapted, the subject is then suddenly placed in scotopic conditions.

c. A series of flashes of light of gradually increasing intensity, localized 11° below fixation, is then presented.

d. The threshold at which the subject just perceives the light is plotted.

e. The flashes are repeated at regular intervals: the sensitivity of the eye to light gradually increases.

2. The sensitivity curve is bipartite (Fig. 15.5).

- The initial rapid segment represents cone function and the second, slower segment rod function.

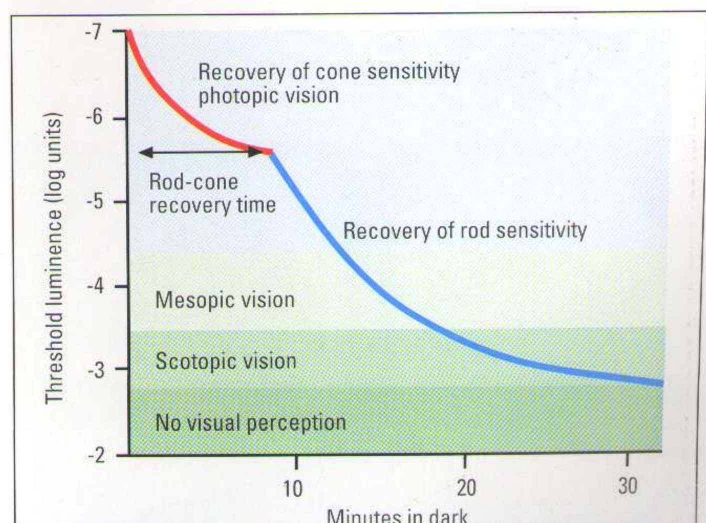


Fig. 15.5
Dark adaptation curve

- The inflection on the curve where rod adaptation begins is called the rod–cone break (alpha point) and in the normal subject occurs 7–10 minutes after exposure to a scotopic environment.
- If the flashes are focused onto the foveola (where rods are absent), only a rapid segment, corresponding to cone adaptation is recorded.

Colour vision

Assessment of colour vision (CV) is sometimes useful in the clinical evaluation of hereditary fundus dystrophies, where impairment may be present prior to the development of visual acuity and visual field changes.

General principles

CV is a function of three populations of retinal cones each with its specific sensitivity: blue (tritan) at 414–424 nm, green (deuteran) 522–539 nm and red (protan) at 549–570 nm. A normal person requires all these primary colours to match those within the spectrum. Any given cone pigment may be deficient (e.g. protanomaly: red weakness) or entirely absent (e.g. protanopia: red blindness). Trichromats possess all three types of cones (although not necessarily functioning perfectly) while absence of one or two types of cones renders an individual a dichromat or a monochromat respectively. Most individuals with congenital colour defects are anomalous trichromats and use abnormal proportions of the three primary colours to match those in the light spectrum. Those with red–green deficiency caused by abnormality of red-sensitive cones are protanomalous, those with abnormality of green-sensitive cones are deuteranomalous and those with blue–green deficiency caused by abnormality of blue-sensitive cones are tritanomalous.

> ***NB:*** Acquired macular disease tends to produce blue–yellow defects and optic nerve lesions red–green defects.

Colour vision tests

1. **Ishihara** test is used mainly to screen for congenital protan and deuteran defects. It consists of a test plate followed by 16 plates each with a matrix of dots arranged to show a central shape or number which the subject is asked to identify (Fig. 15.6). A colour-deficient person will only be able to identify some of the figures. Inability to identify the test plate (provided visual acuity is sufficient) indicates malingering.
2. **City University** consists of 10 plates each containing a central colour and four peripheral colours (Fig. 15.7). The subject selects the peripheral colour which most closely matches the central colour.
3. **Hardy–Rand–Rittler** is similar to Ishihara but more sensitive since it can detect all three congenital defects.
4. **Farnsworth–Munsell 100-hue** is the most sensitive for both congenital and acquired colour defects but is seldom used in practice. Despite the name it consists of 85 hue caps contained in four separate racks in each of which the two end caps are fixed while the others are loose, so they can be randomized by the examiner (Fig. 15.8).
   a. The subject is asked to rearrange the loose randomized caps 'in their natural' order in one box.
   b. The box is then closed, turned upside down and then opened so that the markers on the inside of the caps become visible.

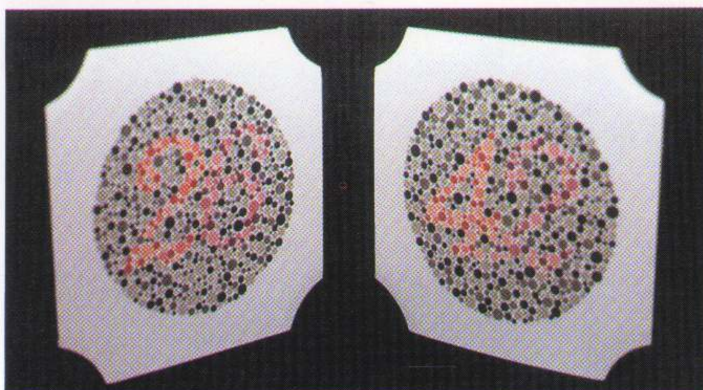


Fig. 15.6
Ishihara pseudo-isochromatic plates

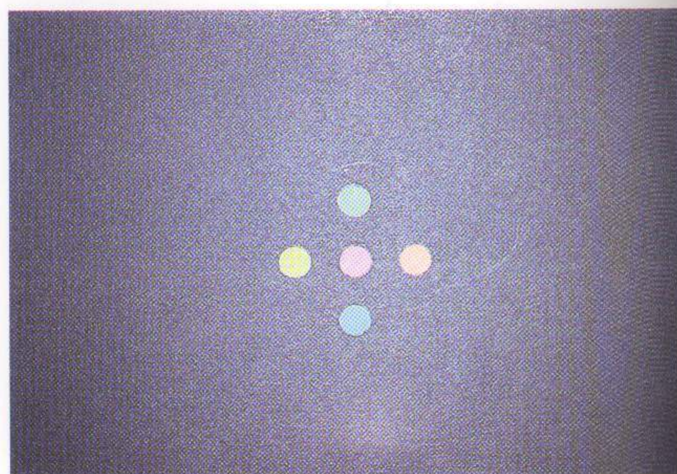


Fig. 15.7
City University test

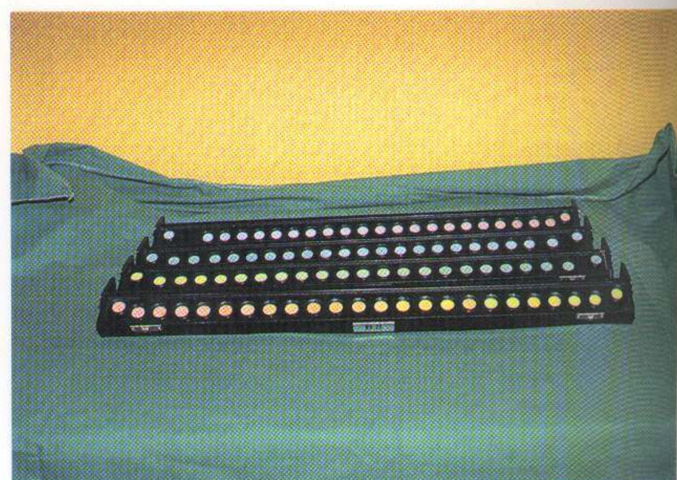


Fig. 15.8
Farnsworth–Munsell 100-hue test

c. The findings are then recorded in a simple cumulative manner on a circular chart.
d. Each of the three forms of dichromatism is characterized by failure in a specific meridian of the chart.

5. **Farnsworth D15** hue discrimination test is similar to the Farnsworth–Munsell 100-hue test but utilizes only 15 caps.

Retinal dystrophies

Retinitis pigmentosa

Retinitis pigmentosa (RP), perhaps better termed pigmentary retinal dystrophy, due to the absence of inflammation, is a diffuse retinal dystrophy predominantly affecting the rod system. Its prevalence is 1:5000.

Inheritance

The age of onset, rate of progression, eventual visual loss and associated ocular features are frequently related to the mode of inheritance. Many cases are due to mutation of the rhodopsin gene. RP may occur as an isolated sporadic disorder, or be inherited in an autosomal dominant (AD), autosomal recessive (AR) or X-linked (XL) manner. It may also be associated with certain systemic disorders which are usually AR.

1. **Isolated**, without any family history, is common.
2. **AD** is also common and has the best prognosis.
3. **AR** is less common and has an intermediate prognosis.
4. **XL** is the least common but most severe. Female carriers may have normal fundi or exhibit a golden-metallic tapetal reflex temporal to the macula and atrophic and pigmentary peripheral irregularities.

Clinical features

Diagnostic criteria for RP are bilateral involvement, loss of peripheral vision and progressive loss of predominantly rod photoreceptor function. The classic clinical triad of RP is (a) *arteriolar attenuation*, (b) *retinal bone-spicule pigmentation* and (c) *waxy disc pallor*.

1. **Presentation** is with nyctalopia during the third decade but may be sooner depending on the pedigree.
2. **Signs** (in chronological order)
   - Arteriolar narrowing, fine dust-like intraretinal pigmentation and loss of RPE, an appearance previously referred to as RP *sine pigmento* (Fig. 15.9). A minority of patients have scattered white dots, most numerous at the equator; this is referred to as *retinitis punctata albescens* (Fig. 15.10).
   - Mid-peripheral, coarse, perivascular 'bone-spicule' pigmentary changes (Fig. 15.11).
   - Gradual increase in density of the pigmentary changes with spread anteriorly and posteriorly (Fig. 15.12).

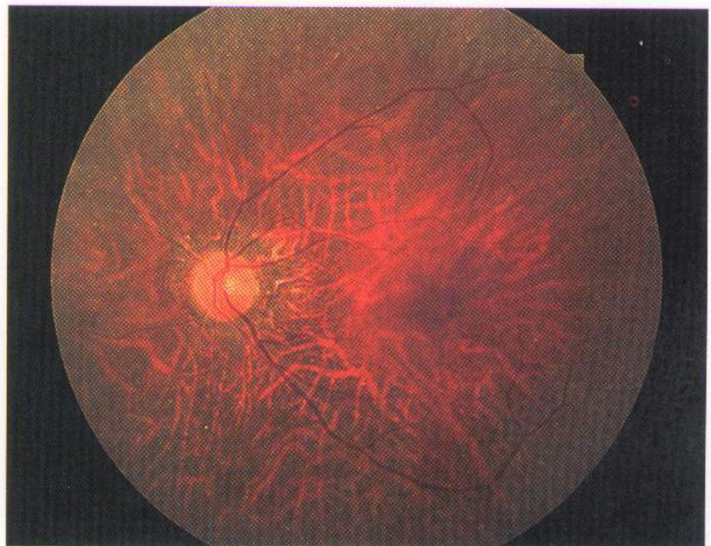


Fig. 15.9
Retinitis pigmentosa with vascular attenuation and minimal pigmentary changes

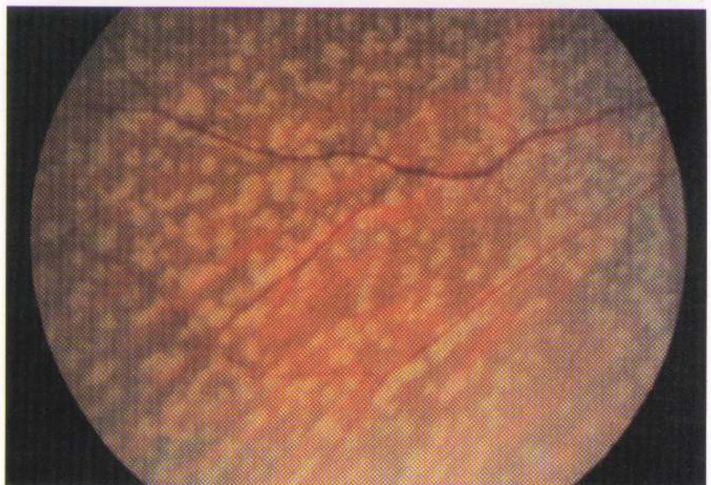




Fig. 15.10
Retinitis punctata albescens

   - Tessellated fundus appearance, due to RPE atrophy and unmasking of large choroidal vessels, severe arteriolar attenuation and waxy disc pallor (Fig. 15.13).

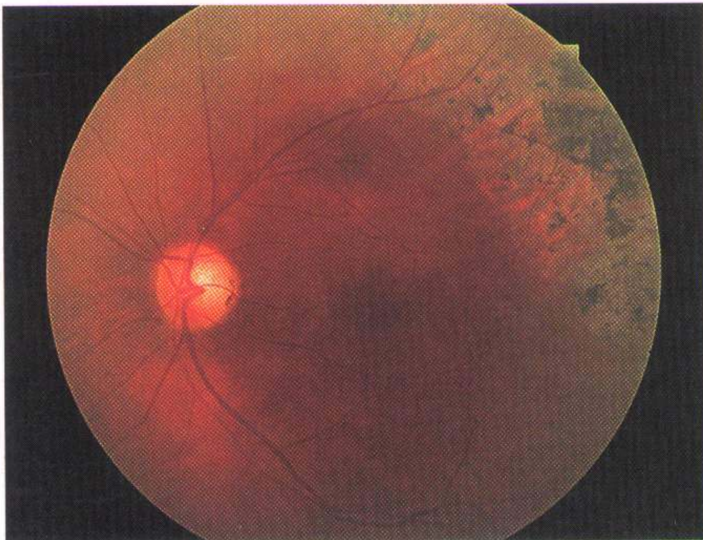


Fig. 15.11
'Bone spicule' pigmentary changes in retinitis pigmentosa



Fig. 15.12
Advanced retinitis pigmentosa

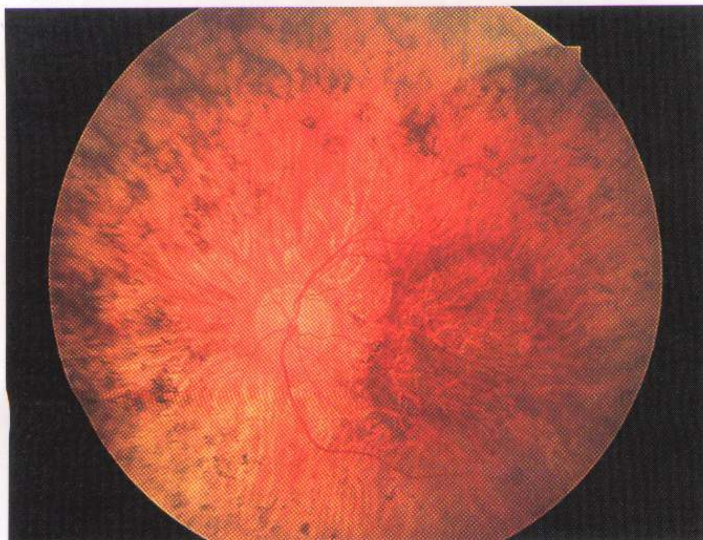


Fig. 15.13
Advanced retinitis pigmentosa with unmasking of choroidal vessels

3. **Maculopathy** may be atrophic, cellophane or CMO; the latter may respond to systemic acetazolamide.

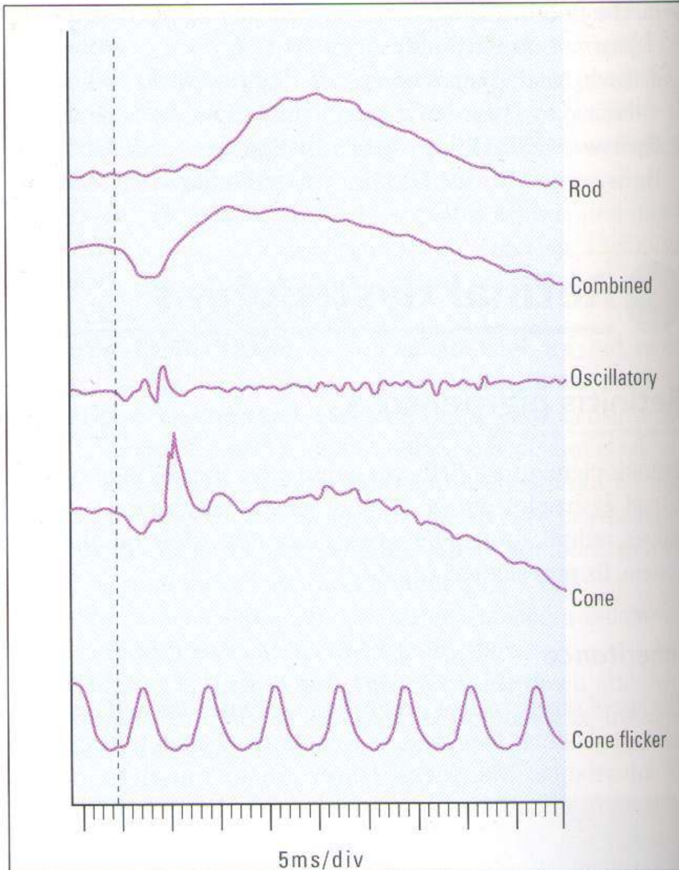


Fig. 15.14
Electroretinogram in retinitis pigmentosa (*see text*)

4. **ERG** initially shows reduced scotopic rod and combined responses (Fig. 15.14): later photopic responses become reduced.
5. **EOG** is subnormal.
6. **DA** is prolonged and may be useful in early cases where the diagnosis is uncertain.
7. **CV** is normal.
8. **Perimetry** classically demonstrates an annular mid-peripheral scotoma, which expands both peripherally and centrally. It ultimately leaves a tiny island of central vision which may eventually be extinguished.
9. **FA**, not required to make the diagnosis, shows diffuse hyperfluorescence due to window defects and small areas of hypofluorescence corresponding to masking by pigment (Fig. 15.15b).

Prognosis

The long-term prognosis is poor, with eventual loss of central vision due to direct involvement of the fovea by RP itself or maculopathy. Daily administration of supplemental vitamin A, if instituted early, may retard the progression of RP. The overall prognosis is as follows:

- About 25% of patients maintain good visual acuity and are able to read throughout their working lives, despite unrecordable ERG and 2–3° central field.
- Under the age of 20 years, most patients have a visual acuity better than 6/60.

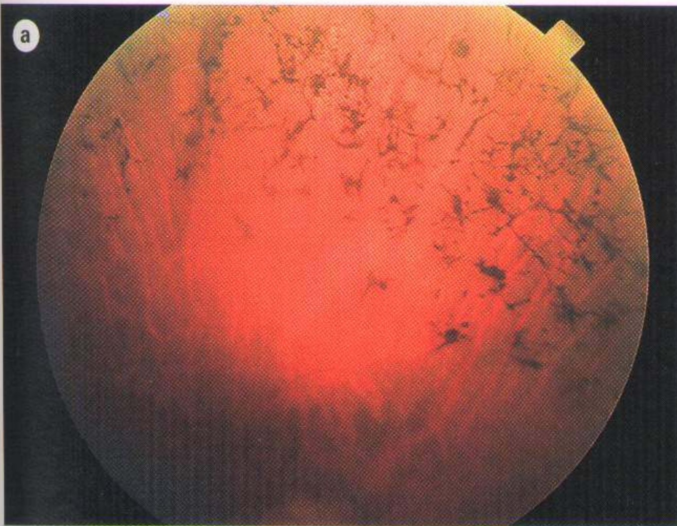




Fig. 15.15
(**a**) Retinitis pigmentosa; (**b**) FA showing diffuse hyperfluorescence due to window defects and focal hypofluorescence due to masking by pigment

- By the age of 50 years an appreciable number have a visual acuity of worse than 6/60.

Ocular associations

Regular follow-up of patients with RP is essential to detect other vision-threatening complications, some of which may be amenable to treatment.

1. **Posterior subcapsular cataracts** are common in all forms of RP; surgery is often beneficial.
2. **Open-angle glaucoma** occurs in 3% of patients.
3. **Myopia** is frequent.
4. **Keratoconus** is uncommon.
5. **Vitreous changes**, which are common, consist of posterior vitreous detachment and occasionally intermediate uveitis.
6. **Optic disc drusen** are more frequently seen than in normals (Fig. 15.16).

Atypical RP

1. **Sector RP** is characterized by involvement of one quadrant (usually nasal) (Fig. 15.17) or one half (usually inferior). Progression is slow and many cases remain stationary.
2. **Pericentral RP** in which the pigmentary abnormalities emanate from the disc and extend along the temporal arcades and nasally.
3. **RP with exudative vasculopathy** is characterized by a Coats-like appearance with lipid deposition in the peripheral retina and exudative retinal detachment.

Differential diagnosis

1. **End-stage chloroquine retinopathy**
   - Similarities: bilateral diffuse loss of RPE with unmasking of choroidal vessels and arteriolar attenuation.

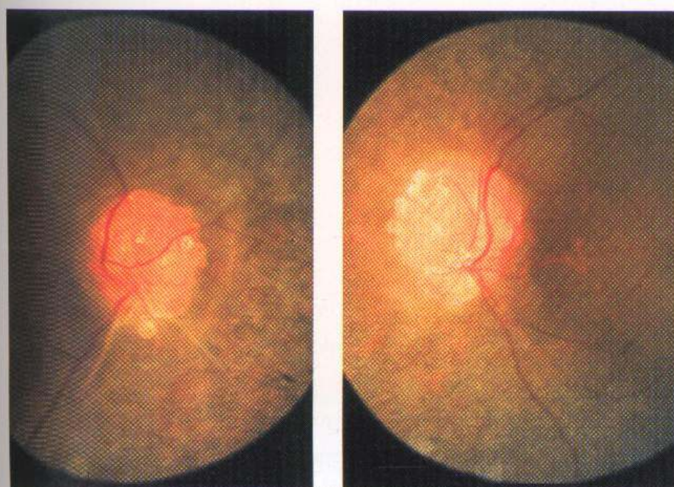


Fig. 15.16
Optic disc drusen associated with retinitis pigmentosa

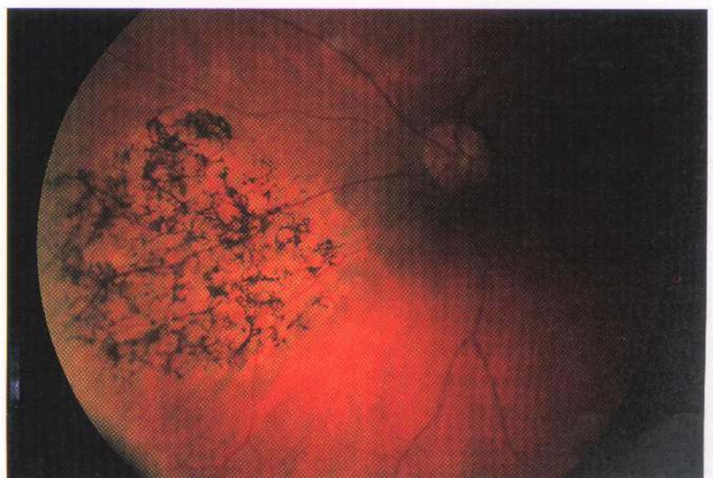


Fig. 15.17
Sector retinitis pigmentosa

- Differences: pigmentary changes do not have a perivascular 'bone corpuscle' configuration; optic atrophy is not waxy.

2. **End-stage thioridazine retinopathy**
   - Similarities: bilateral diffuse loss of RPE.
   - Differences: plaque-like pigmentary changes and absence of nyctalopia.
3. **End-stage syphilitic neuroretinitis**
   - Similarities: gross restriction of visual fields, vascular attenuation and pigmentary changes.
   - Differences: nyctalopia is mild, asymmetrical involvement with mild or absent choroidal unmasking.
4. **Cancer-related retinopathy**
   - Similarities: nyctalopia, restriction of peripheral visual field, arteriolar attenuation and extinguished ERG.
   - Differences: more rapid course and mild or absent pigmentary changes.

Systemic associations

RP, often atypical, may be associated with a wide variety of systemic disorders. The more important associations are described hereunder.

1. **Bassen–Kornzweig syndrome** is an AD disease due to deficiency in beta-lipoprotein resulting in intestinal malabsorption.
   a. *Signs*. Spinocerebellar ataxia and acanthocytosis in peripheral blood.
   b. *Retinopathy* develops towards the end of the first decade; the pigment clumps are often larger than in classic RP and are not confined to the equatorial region. Peripheral white dots are also common.
   c. *Other features* are ophthalmoplegia and ptosis.
   d. *Treatment* with vitamin E, if instituted early, may be beneficial for neurological disability.
2. **Refsum disease** is an AR inborn error of metabolism due to a deficiency in the enzyme phytanic acid 2-hydroxylase resulting in the accumulation of phytanic acid in the blood and body tissues.
   a. *Signs* include polyneuropathy, cerebellar ataxia, deafness, anosmia, cardiomyopathy, ichthyosis and elevated CSF protein in the absence of pleocytosis (cytoalbuminous inversion).
   b. *Retinopathy* develops in the second decade and is characterized by generalized 'salt-and-pepper' changes.
   c. *Other features* include cataract, miosis and prominent corneal nerves.
   d. *Treatment*, initially with plasmapheresis and later with a phytanic-acid-free diet, may prevent progression of both systemic and retinal involvement.
3. **Usher syndrome** is a distressing AR condition which accounts for about 5% of all cases of profound deafness in children, and is responsible for about half of all cases of combined deafness and blindness. RP develops before puberty.

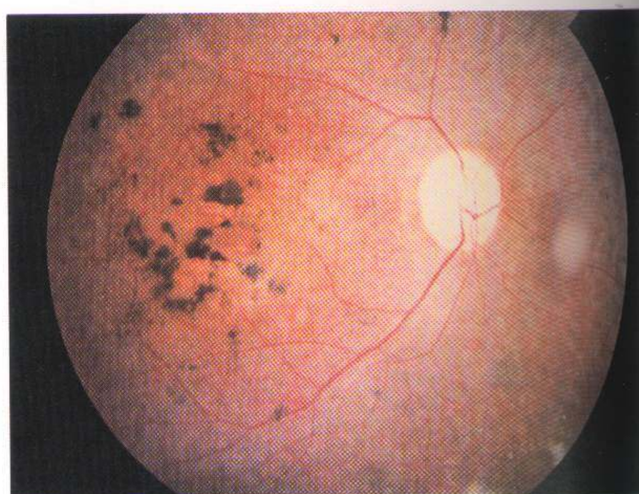


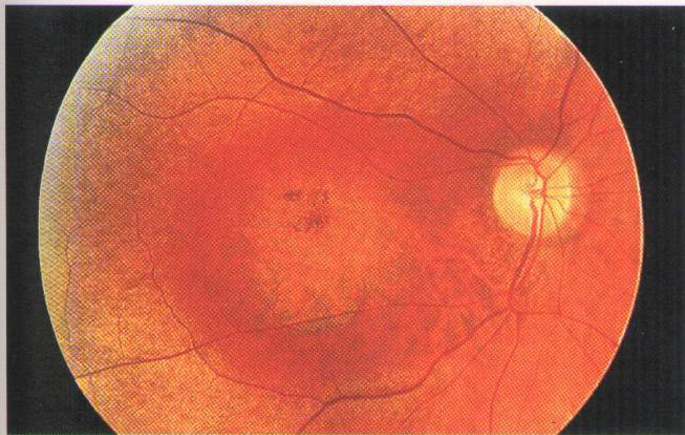
Fig. 15.18
Central retinitis pigmentosa in Kearns–Sayre syndrome

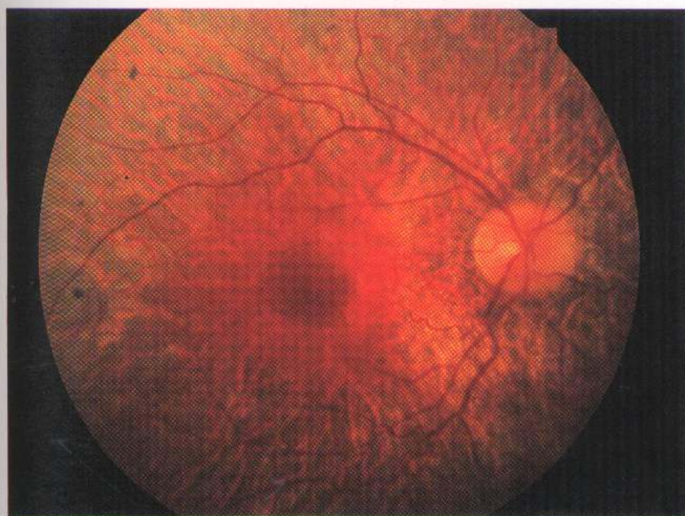
4. **Kearns–Sayre syndrome** is a mitochondrial cytopathy associated with mitochondrial DNA deletions (*see* Chapter 20). Atypical RP is characterized by coarse pigment clumping which principally affects the central fundus (Fig. 15.18).
5. **Bardet–Biedl syndrome** is characterized by mental handicap, polydactyly, obesity and hypogenitalism. RP is serious and almost 75% of patients are blind by the age of 20 years. Some patients develop a bull's eye maculopathy.

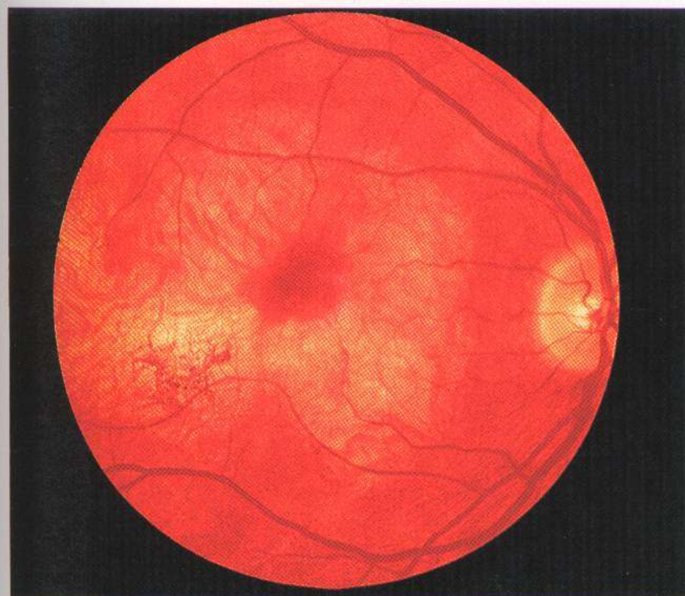
Progressive cone dystrophy

Progressive cone dystrophies comprise a heterogeneous group of rare disorders. Patients with pure cone dystrophy initially have only cone dysfunction. Those with cone–rod dystrophy have an associated but less severe rod dysfunction. However, in many patients with initially pure cone dysfunction the rod system becomes subsequently affected. The term 'cone–rod dystrophy' is therefore more appropriate.

1. **Inheritance**. Most cases are sporadic; of the remainder, the most frequent established inheritance pattern is AD, but the condition may also be AR or XL.
2. **Presentation** is in the first to third decades with gradual bilateral impairment of central and colour vision which may later be associated with photophobia and fine pendular nystagmus.
3. **Signs** (in chronological order)
   - The fovea may be normal or exhibit non-specific granularity.
   - Bull's eye maculopathy (Fig. 15.19) is classically described but not universal.
   - Mid-peripheral 'bone-spicule' pigmentation, arteriolar attenuation and temporal disc pallor may develop (Fig. 15.20).


Fig. 15.19
Cone dystrophy with 'bull's eye' maculopathy


Fig. 15.20
Cone dystrophy with mild 'bone-spicule' pigmentary changes


Fig. 15.21
Advanced cone dystrophy with atrophic maculopathy

- Progressive RPE atrophy at the macula with eventual geographic atrophy (Fig. 15.21).

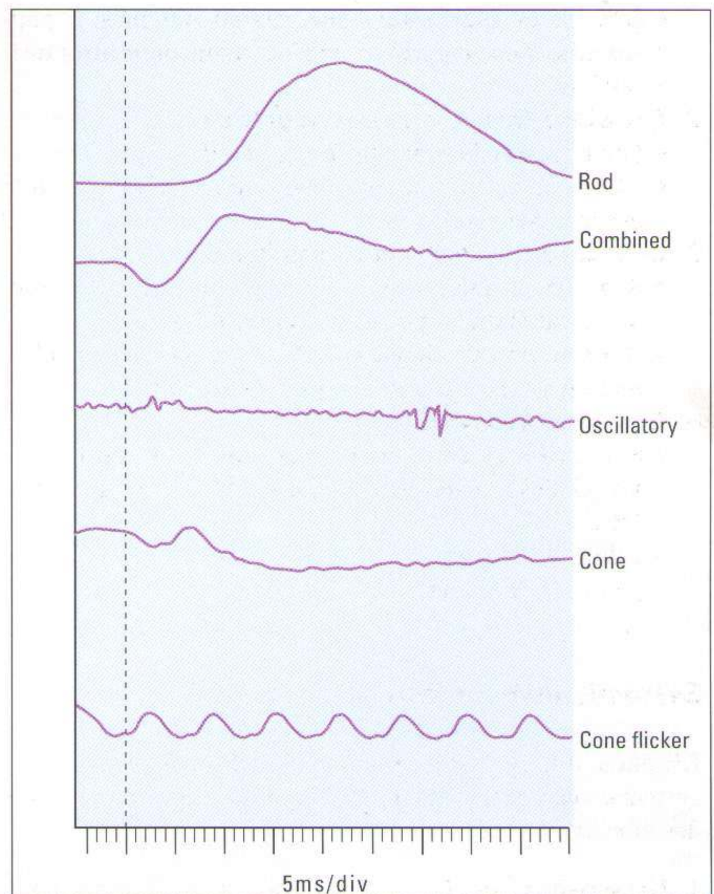
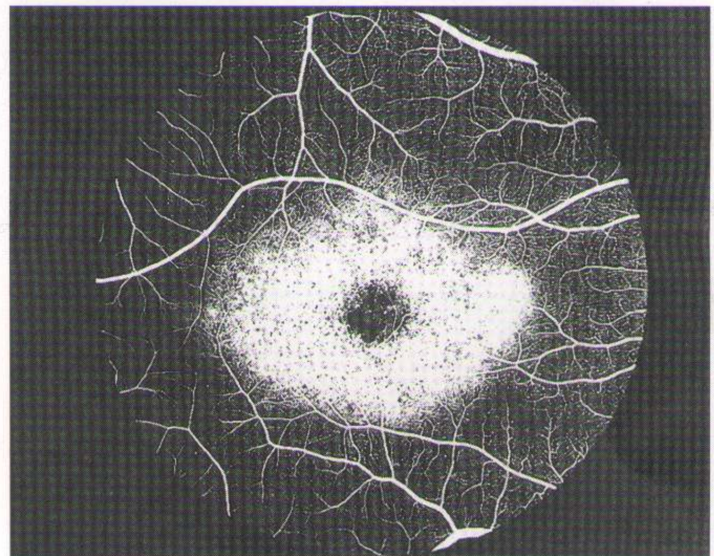


Fig. 15.22
Electroretinogram in cone dystrophy (*see text*)


Fig. 15.23
FA in cone dystrophy showing a 'bull's eye' pattern due to a window defect

4. **ERG**. Photopic is abnormal or non-recordable; flicker fusion frequency is reduced; rod responses are preserved until late (Fig. 15.22).
5. **EOG** is normal to subnormal.
6. **DA**. Cone segment is abnormal; rod segment is initially normal but may become subnormal later.
7. **CV** shows a severe deuteran–tritan defect out of proportion to visual acuity.

8. **FA** of bull's eye maculopathy shows a round hyperfluorescent window defect with a hypofluorescent centre (Fig. 15.23).
9. **Prognosis** depends on the severity of rod involvement; minimal involvement has a better prognosis, at least in the intermediate term.
10. **Differential diagnosis** of bull's eye macula includes chloroquine maculopathy, advanced Stargardt disease, fenestrated sheen dystrophy, benign concentric annular macular dystrophy and Batten disease.

Stargardt disease

Stargardt disease (juvenile macular dystrophy) and fundus flavimaculatus are regarded as variants of the same disease despite presenting at different times and carrying different prognoses.

1. **Inheritance** is AR with the gene locus ABC4R on 1p21–22.
2. **Presentation** is in the first to second decades with bilateral, gradual impairment of central vision which may be out of proportion to the macular changes, so that the child may be suspected of malingering.
3. **Signs** (in chronological order)
   - The fovea may be normal or show non-specific mottling (Fig. 15.24).
   - Oval, 'snail-slime' or 'beaten-bronze' foveal appearance, which may be surrounded by yellow-white flecks (Fig. 15.25).
   - Geographic atrophy which may have bull's eye configuration (Fig. 15.26).
4. **ERG**. Photopic is normal to subnormal; scotopic is normal.
5. **EOG** is subnormal in advanced cases.
6. **CV** shows deuteran–tritan defects.

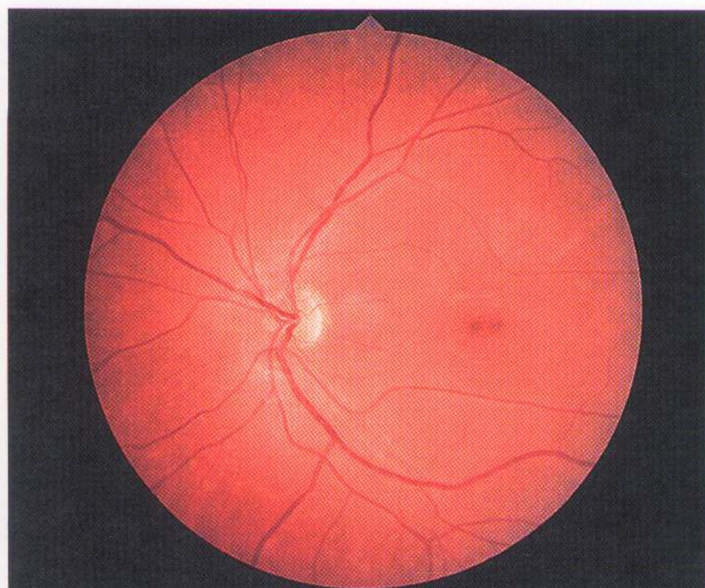


Fig. 15.24
Early Stargardt macular dystrophy

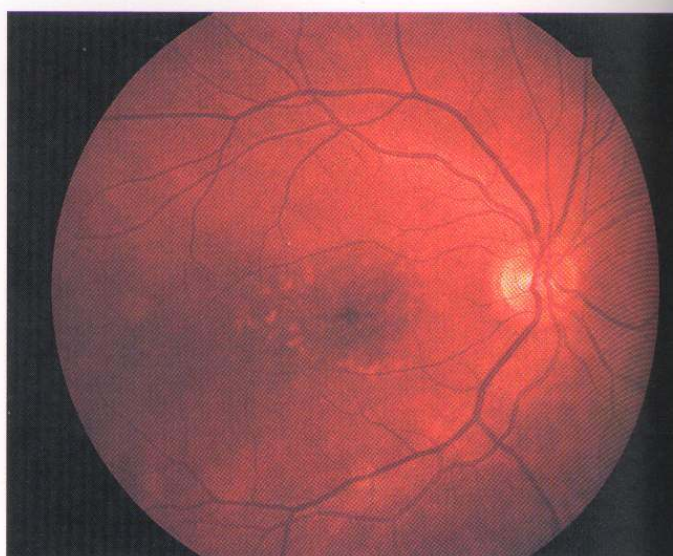


Fig. 15.25
Stargardt macular dystrophy with surrounding flecks

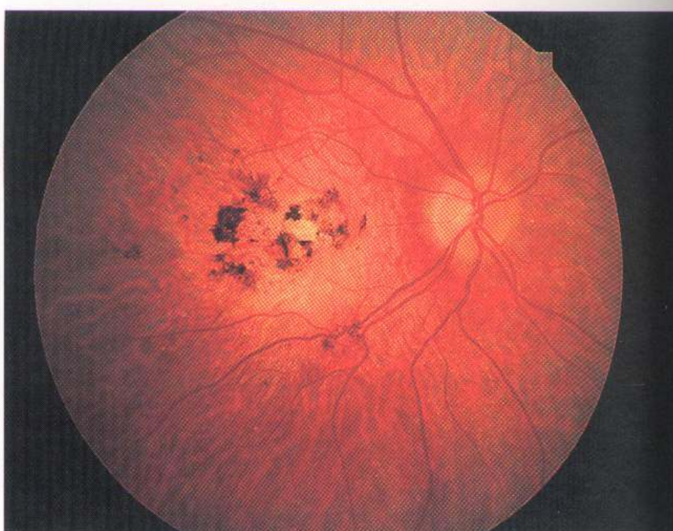


Fig. 15.26
Advanced Stargardt macular dystrophy

7. **FA** often shows a 'dark choroid' due to lipofuscin deposits within the RPE. It is characterized by absence of normal background fluorescence, which enhances the prominence of the retinal circulation. Eyes with geographic atrophy show a window defect at the macula (Fig. 15.27).
8. **Prognosis** is poor; once visual acuity drops below 6/12 it tends to decrease rapidly and stabilize at about 6/60.

Fundus flavimaculatus

1. **Inheritance** is AR.
2. **Presentation** is in adult life, although in the absence of macular involvement the condition may be asymptomatic and discovered by chance.
3. **Signs** (in chronological order)
   - Bilateral, ill-defined, yellow-white flecks, at the level of the RPE, scattered throughout the posterior pole and

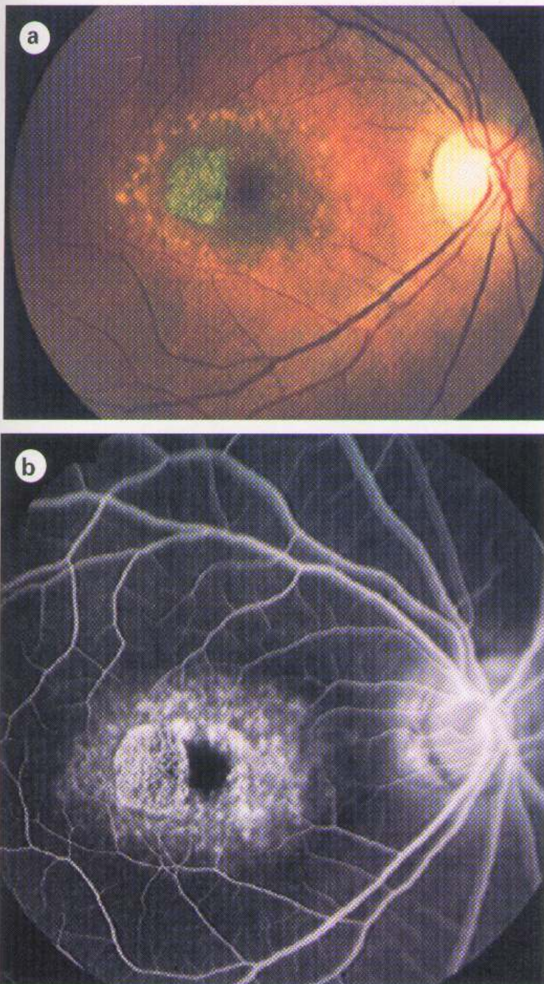


Fig. 15.27
(**a**) Stargardt macular dystrophy; (**b**) FA showing macular hyperfluorescence due to a window defect and a dark choroid (Courtesy of S. Milewski)

mid-periphery. The flecks may be round, oval, linear, semilunar or pisciform (fish-tail-like) (Fig. 15.28).
- The fundus has a vermilion colour in about 50% of cases.
- New lesions develop as older ones become ill-defined and softer (*see* Fig. 15.30a).
- Geographic atrophy develops in some cases (Fig. 15.29).

4. **ERG**. Photopic is normal to subnormal; scotopic is normal.
5. **EOG** is subnormal.
6. **CV** is normal.
7. **FA** shows a generalized 'dark choroid'. Fresh flecks show early blockage and late staining; old flecks show RPE window defects (Fig. 15.30b).
8. **Prognosis** is relatively good and patients may remain asymptomatic for many years unless one of the flecks involves the foveola or geographic atrophy develops.
9. **Differential diagnosis** of retinal flecks includes dominant drusen, fundus albipunctatus, early North Carolina macular dystrophy and benign fleck retina syndrome.

Juvenile Best disease

Juvenile Best disease (vitelliform dystrophy) is a rare condition which evolves gradually through five stages.

1. **Inheritance** is AD with variable penetrance and expressivity with the gene locus on 11q13.
2. **Stage 0** (pre-vitelliform) is characterized by a subnormal EOG in an asymptomatic child with a normal fundus appearance.
3. **Stage 1** is characterized by pigment mottling at the macula.

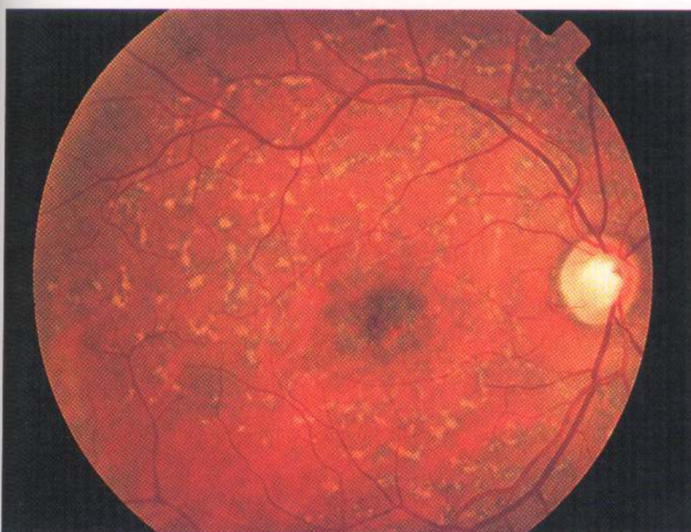


Fig. 15.28
Fundus flavimaculatus (Courtesy of S. Milewski)

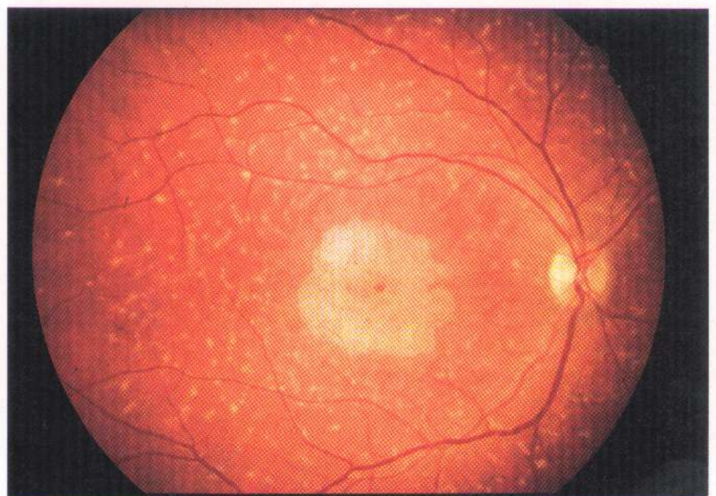
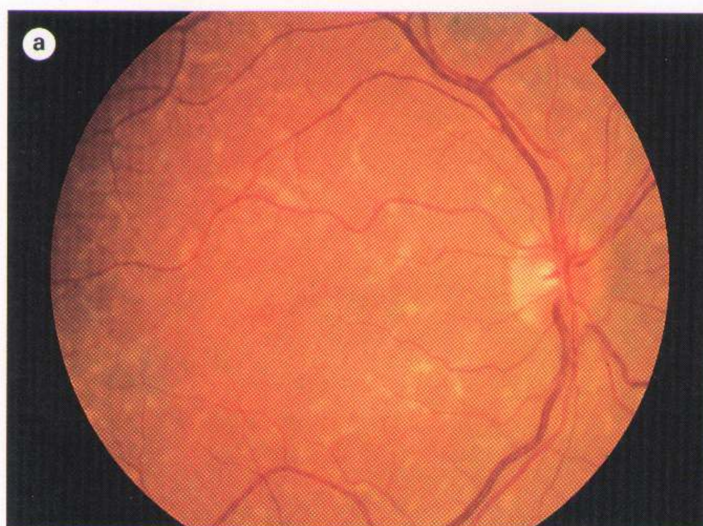


Fig. 15.29
Fundus flavimaculatus with atrophic maculopathy (Courtesy of S. Milewski)



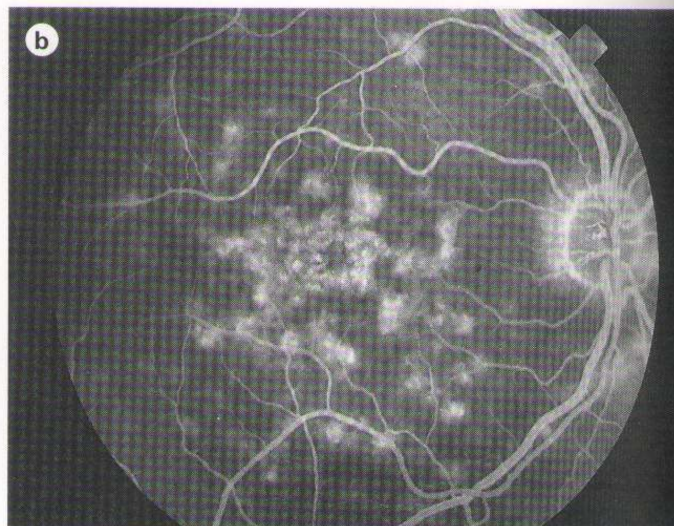
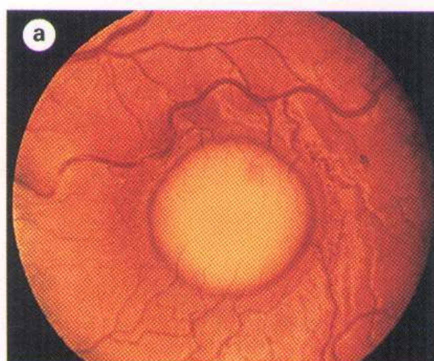


Fig. 15.30
(**a**) Advanced fundus flavimaculatus; (**b**) FA showing hyperfluorescence of the flecks and a dark choroid (Courtesy of S. Milewski)



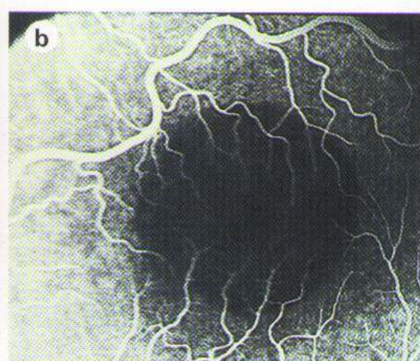


Fig. 15.31
(**a**) Vitelliform stage of juvenile Best disease; (**b**) FA showing hypofluorescence due to blocked background choroidal fluorescence (Courtesy of Wilmer Institute)

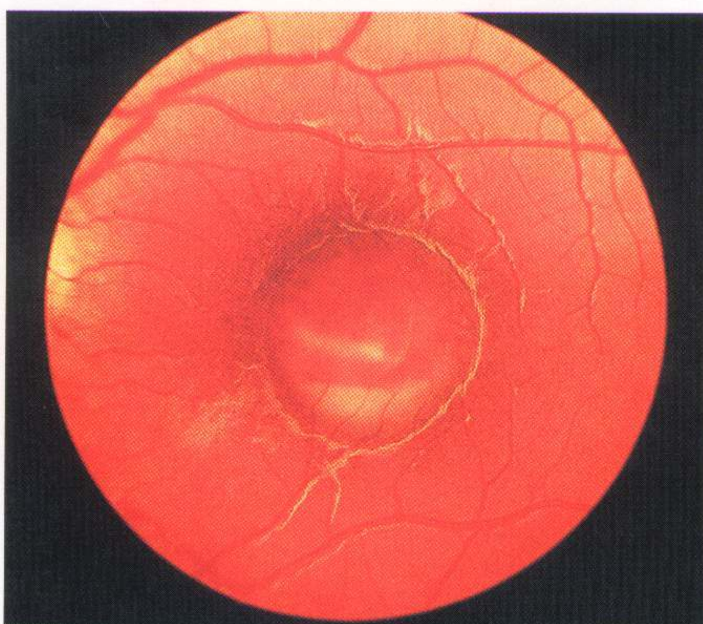


Fig. 15.32
Pseudo-hypopyon stage of juvenile Best disease (Courtesy of P. Morse)

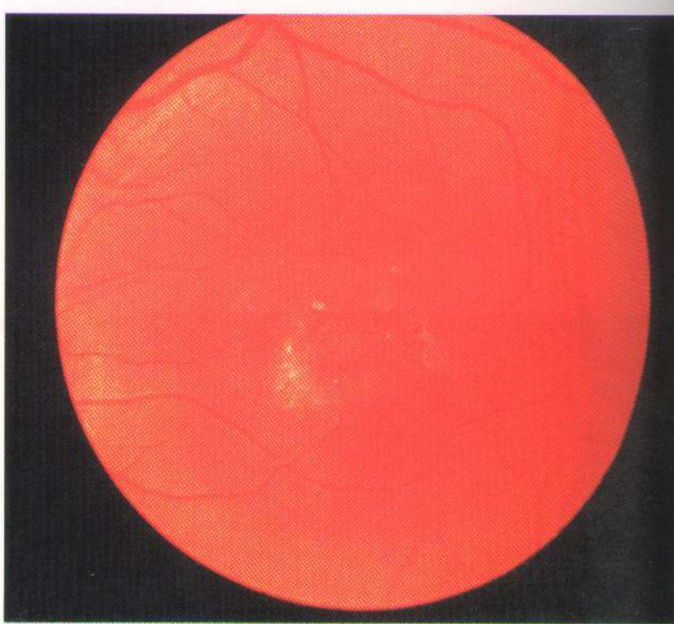


Fig. 15.33
Vitelliruptive stage of juvenile Best disease (Courtesy of P. Morse)

4. **Stage 2** (vitelliform), which develops in the first to second decades, is characterized by a round egg-yolk ('sunny side up') macular lesion consisting of subretinal lipofuscin (Fig. 15.31a). Visual acuity may be normal or slightly decreased.
5. **Stage 3** (pseudo-hypopyon) may occur when part of the lesion becomes absorbed (Fig. 15.32). Occasionally, the whole lesion becomes absorbed with little effect on vision.
6. **Stage 4** (vitelliruptive) in which the egg yolk begins to break up ('scrambled egg') (Fig. 15.33) and visual acuity drops.

7. **ERG** is normal.
8. **EOG** is severely subnormal during all stages and in carriers with normal fundi.
9. **CV** defects are proportional to the degree of visual loss.
10. **FA** during the vitelliform stage shows blockage of background choroidal fluorescence (*see* Fig. 15.31b).
11. **Prognosis** is reasonably good until the fifth decade, after which visual acuity declines and some patients become legally blind due to macular scarring, CNV, geographic atrophy or hole formation which may lead to retinal detachment.

Adult vitelliform foveomacular dystrophy

Adult vitelliform foveomacular dystrophy is considered as belonging to the category of 'pattern dystrophies'. In contrast to juvenile Best disease the foveal lesions are smaller, present later and do not demonstrate evolutionary changes.

1. **Inheritance** is probably AD with the gene locus on 6p21–22.
2. **Presentation** is in the fourth to sixth decades with mild metamorphopsia although often the condition is discovered by chance.
3. **Signs**. Bilateral, symmetrical, round, slightly elevated, yellow, subfoveal lesions about one-third disc diameter in size (Fig. 15.34).
4. **ERG** is normal.
5. **EOG** is normal to moderately subnormal.
6. **CV** shows a mild tritan defect.
7. **FA** shows central hypofluorescence surrounded by a small irregular hyperfluorescent ring.
8. **Prognosis** is good in the majority of cases.

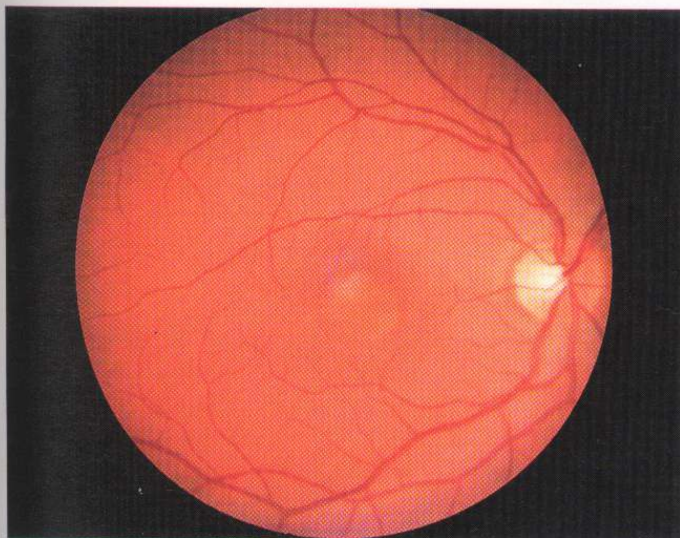


Fig. 15.34
Adult vitelliform macular dystrophy

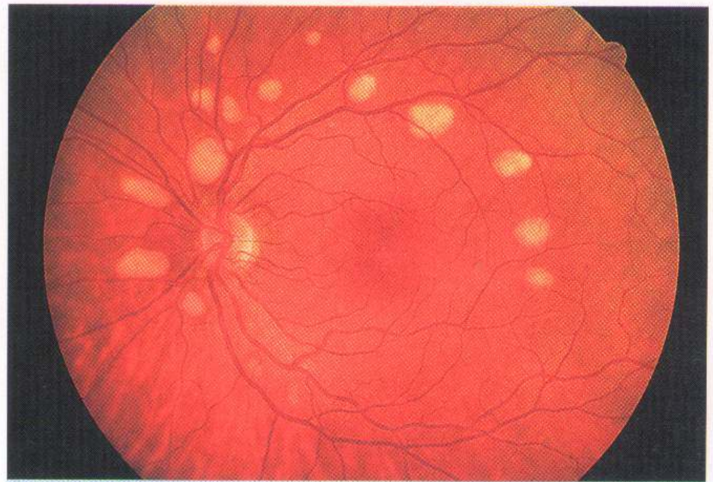


Fig. 15.35
Multifocal Best disease (Courtesy of C. Barry)

Multifocal Best disease

Multifocal Best disease is very unusual (Fig. 15.35) and may occur without a family history. It may develop acutely in adult life and give rise to diagnostic difficulties.

Familial drusen

Familial drusen (Doyne honeycomb choroiditis, malattia levantinese) is thought to represent an early manifestation of age-related macular degeneration.

1. **Inheritance** is AD with full penetrance but variable expressivity. The gene locus EFEMP1 is on 2p16.
2. **Clinical features**
   a. *Mild* disease is characterized by a few small, discrete, hard drusen confined to the macula (Fig. 15.36). The lesions typically appear in the third decade and are innocuous.

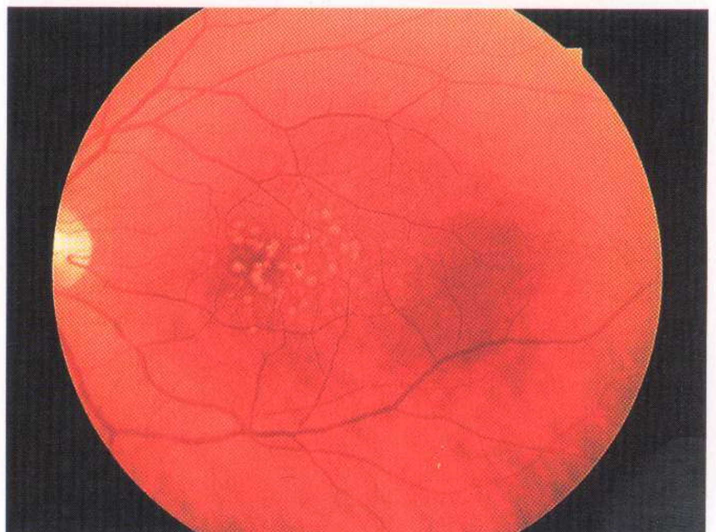


Fig. 15.36
Mild familial dominant drusen

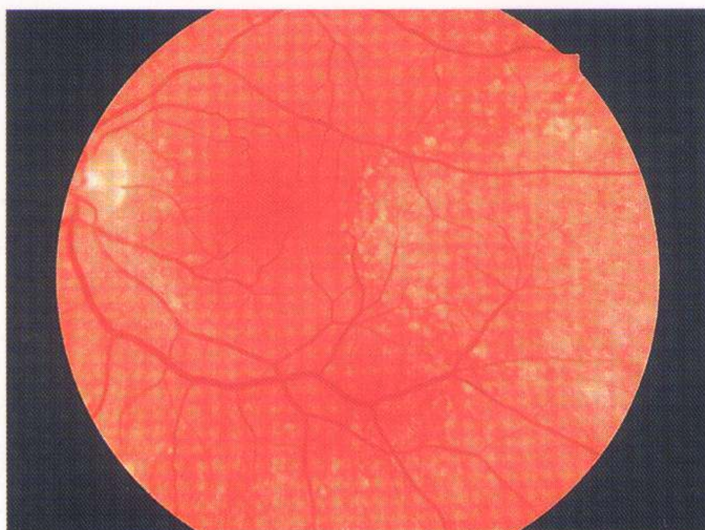


Fig. 15.37
Advanced familial dominant drusen

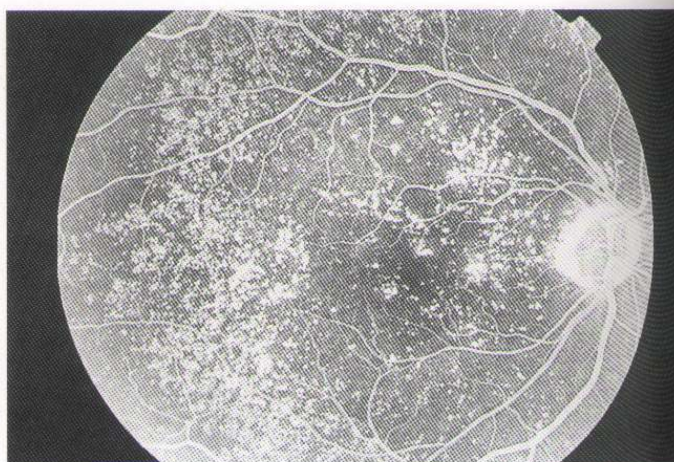


Fig. 15.39
FA in familial dominant drusen showing numerous well-defined hyperfluorescent spots

   b. *Moderate* disease is characterized by large, soft drusen at the posterior pole and parapapillary region (Fig. 15.37). The lesions appear after the third decade and are associated with normal or mild impairment of visual acuity.
   c. *Advanced* disease is uncommon and presents after the fifth decade with CNV or geographic atrophy.
   d. *Malattia leventinese* shares phenotypic overlap with familial drusen. It is characterized by small, innumerable, basal laminar drusen with a spoke-like or radial distribution centred on the fovea and parapapillary area (Fig. 15.38). Most patients are asymptomatic until the fourth to fifth decades, when they may develop CNV or geographic atrophy.

3. **ERG** is normal.
4. **EOG** is subnormal in patients with advanced disease.
5. **FA** shows well-defined hyperfluorescent spots due to window defects which are more extensive on FA (Fig. 15.39) than on clinical examination.

Sorsby pseudo-inflammatory macular dystrophy

Sorsby pseudo-inflammatory macular dystrophy, also referred to as hereditary haemorrhagic macular dystrophy, is a very rare but serious condition.

1. **Inheritance** is AD with full penetrance; the gene TIMP3 is on 22q12.1–13.2.
2. **Presentation** is in the fifth decade with bilateral exudative maculopathy.
3. **Signs** (in chronological order)
   - Yellow-white, confluent, drusen-like deposits along the arcades, nasal to the disc and mid-periphery (Fig. 15.40).
   - CNV and exudative maculopathy (Fig. 15.41).
   - Subretinal scarring (Fig. 15.42).
4. **ERG** is initially normal but may be subnormal in late disease.

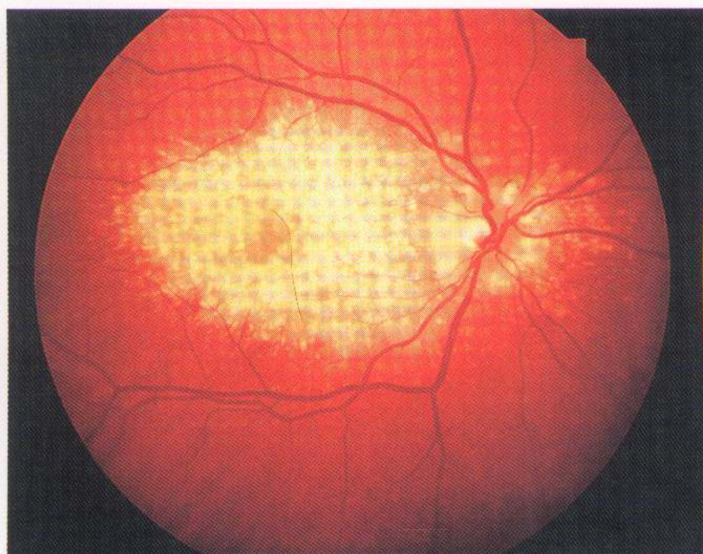


Fig. 15.38
Malattia leventinese (Courtesy of Moorfields Eye Hospital)

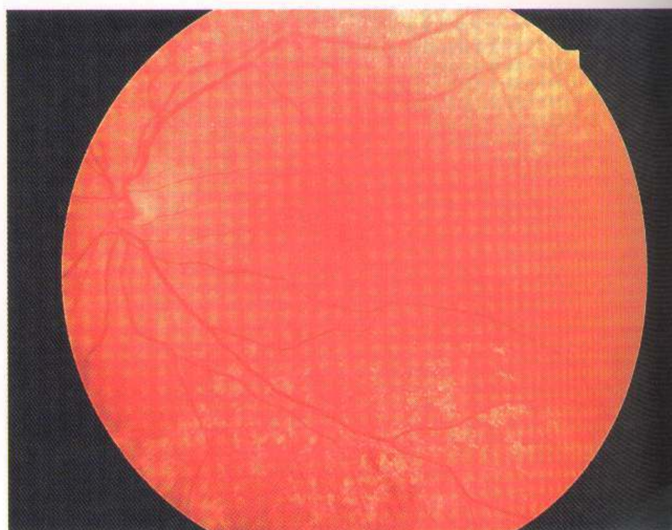
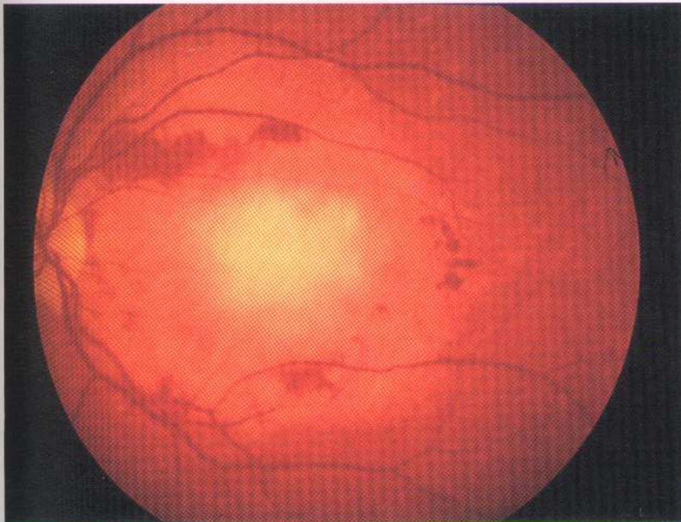
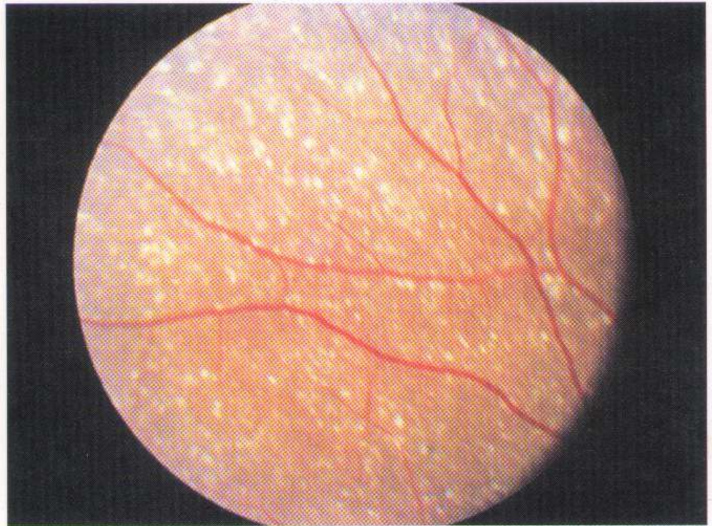
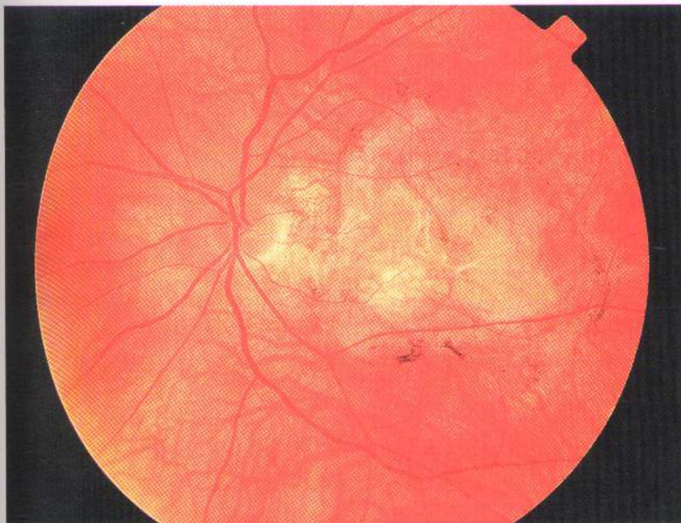
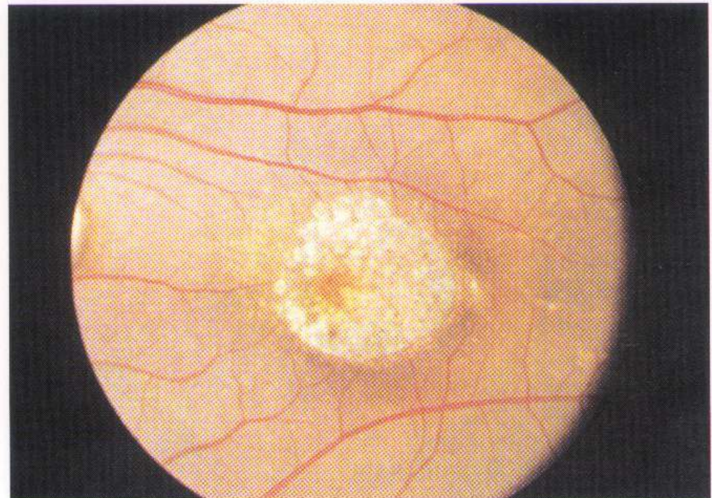


Fig. 15.40
Early Sorsby pseudo-inflammatory macular dystrophy with confluent flecks


Fig. 15.41
Exudative maculopathy in Sorsby pseudo-inflammatory macular dystrophy


Fig. 15.43
Peripheral flecks in grade 1 North Carolina macular dystrophy (Courtesy of P. Morse)


Fig. 15.42
End-stage Sorsby pseudo-inflammatory macular dystrophy


Fig. 15.44
Confluent macular flecks in grade 2 North Carolina macular dystrophy (Courtesy of P. Morse)

5. **EOG** is normal.
6. **Prognosis** is poor due to maculopathy. Some patients also lose ambulatory vision by the seventh decade due to progressive peripheral chorioretinal atrophy.

North Carolina macular dystrophy

North Carolina macular dystrophy is a very rare but serious condition.

1. **Inheritance** is AD with complete penetrance but highly variable expressivity with the gene MCDR1 on 6q.
2. **Signs and prognosis**
   a. *Grade 1* is characterized by yellow-white, drusen-like peripheral (Fig. 15.43) and macular deposits which develop during the first decade and may remain asymptomatic throughout life.
   b. *Grade 2* is characterized by deep, confluent macular deposits (Fig. 15.44). The long-term visual prognosis is less favourable because some patients develop exudative maculopathy.
   c. *Grade 3* is characterized by bilateral coloboma-like atrophic macular lesions (Fig. 15.45) with variable impairment of visual acuity.
3. **ERG** is normal.
4. **EOG** is normal.
5. **FA** in grades 1 and 2 shows transmission defects and late staining.

Butterfly macular dystrophy

Butterfly dystrophy is a rare and relatively innocuous condition.

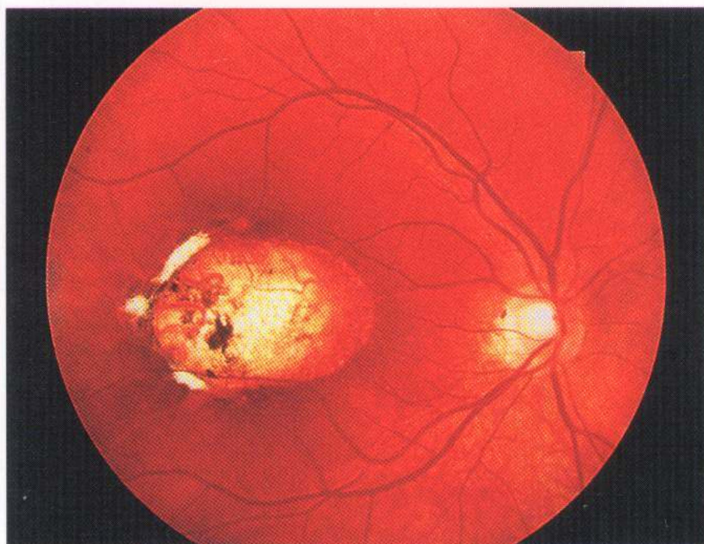


Fig. 15.45
Coloboma-like maculopathy in grade 3 North Carolina macular dystrophy (Courtesy of Moorfields Eye Hospital)

1. **Inheritance** is probably AD.
2. **Presentation** is in the second to fifth decades usually by chance and occasionally with mild impairment of central vision.
3. **Signs**
   - Yellow pigment at the fovea arranged in a triradiate manner (Fig. 15.46).
   - Peripheral pigmentary stippling may be present.
4. **ERG** is normal.
5. **EOG** is subnormal to abnormal.
6. **FA** shows corresponding hypofluorescence.
7. **Prognosis** is excellent.

Dominant cystoid macular oedema

Dominant cystoid macular oedema is an extremely rare but serious condition.

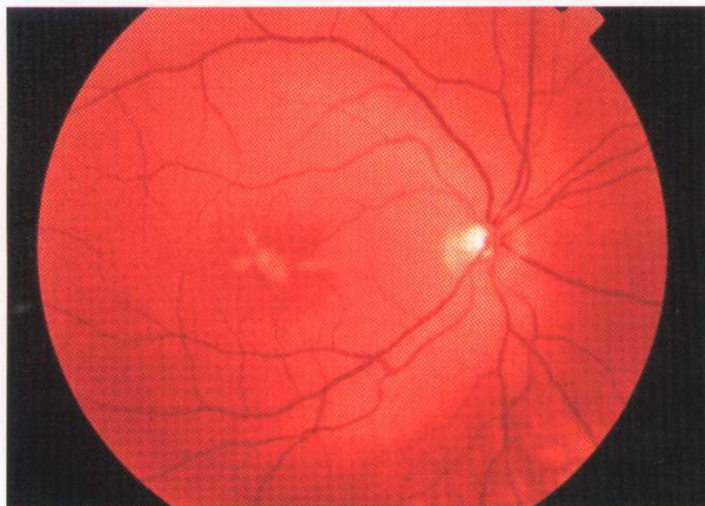


Fig. 15.46
Butterfly dystrophy

1. **Inheritance** is AD with the gene locus on 7q.
2. **Presentation** is in the first to second decades with gradual impairment of central vision.
3. **Signs**. Bilateral CMO which does not respond to systemic acetazolamide.
4. **ERG** is normal.
5. **EOG** is normal to subnormal.
6. **FA** shows a flower-petal pattern of leakage at the fovea (*see* Fig. 13.83).
7. **Prognosis** is poor because of eventual development of geographic atrophy.

Bietti crystalline dystrophy

Bietti crystalline dystrophy is characterized by deposition of crystals in the retina and peripheral cornea.

1. **Inheritance** is XL or AR.
2. **Presentation** is in the third decade with progressive visual loss.
3. **Signs** (in chronological order)
   - Yellow-white crystals scattered throughout the posterior fundus (Fig. 15.47).
   - Localized atrophy of the RPE and choriocapillaris at the macula.
   - Diffuse atrophy of the choriocapillaris.
   - Gradual confluence and expansion of the atrophic areas into the retinal periphery.
4. **ERG** is subnormal.
5. **EOG** is subnormal.
6. **Prognosis** is variable because the rate of disease progression differs in individual cases.

Alport syndrome

Alport syndrome is a rare abnormality of glomerular basement membrane caused by mutations in several different

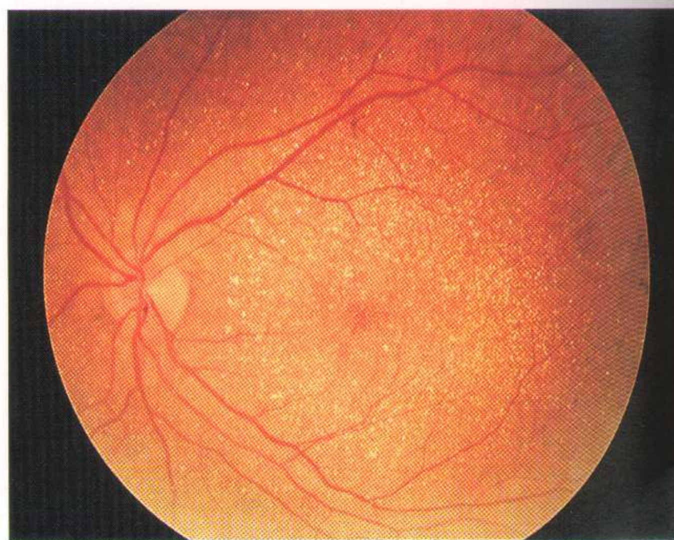


Fig. 15.47
Bietti crystalline dystrophy (Courtesy of J. Salmon)

genes, all of which encode particular forms of type IV collagen, a major component of basement membrane. It is characterized by chronic renal failure, often associated with sensorineural deafness.

1. **Inheritance** is XL dominant.
2. **Signs**
   - Scattered, pale, yellow, punctate flecks in the perimacular area, sparing the fovea, with normal visual acuity (Fig. 15.48).
   - Larger flecks, some of which may become confluent, in the periphery (Fig. 15.49).
3. **ERG** is normal.
4. **Ocular associations** are anterior lenticonus and occasionally posterior polymorphous corneal dystrophy.
5. **Prognosis** is excellent.

Benign familial fleck retina

Benign familial fleck retina is a very rare disorder which is asymptomatic and therefore usually discovered by chance.

1. **Inheritance** is AR.
2. **Signs**
   - Widespread, discrete, yellow-white flecks at the level of the RPE which spare the fovea (Fig. 15.50).
   - The lesions have variable shapes and extend to the far periphery (Fig. 15.51).
3. **ERG** is normal.
4. **Prognosis** is excellent.

Leber congenital amaurosis

Leber congenital amaurosis is a very rare but potentially serious disease with systemic implications.

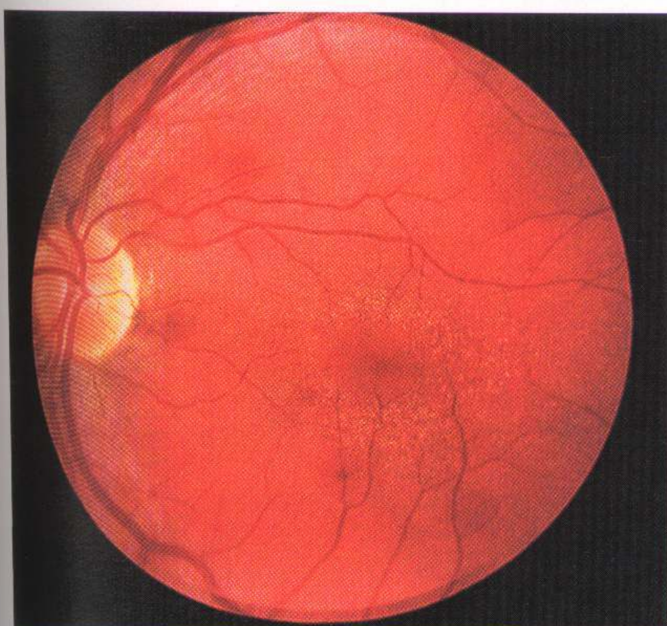


Fig. 15.48
Macular flecks in Alport syndrome (Courtesy of J. Govan)

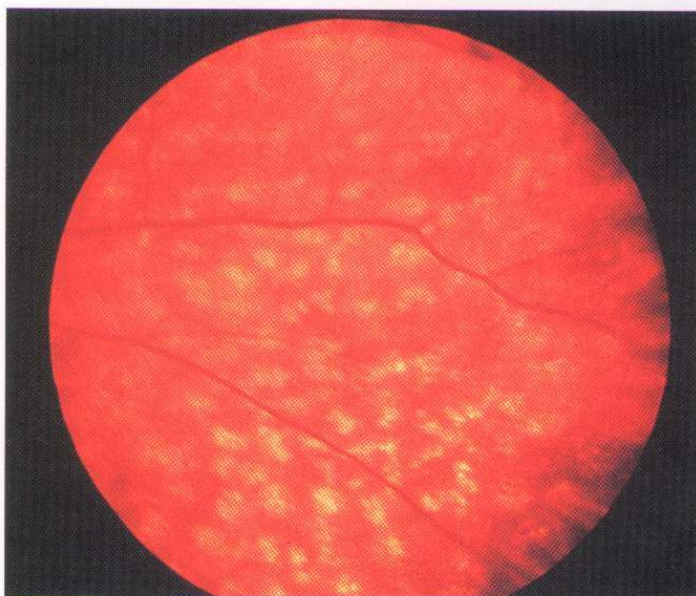


Fig. 15.49
Peripheral flecks in Alport syndrome (Courtesy of J. Govan)

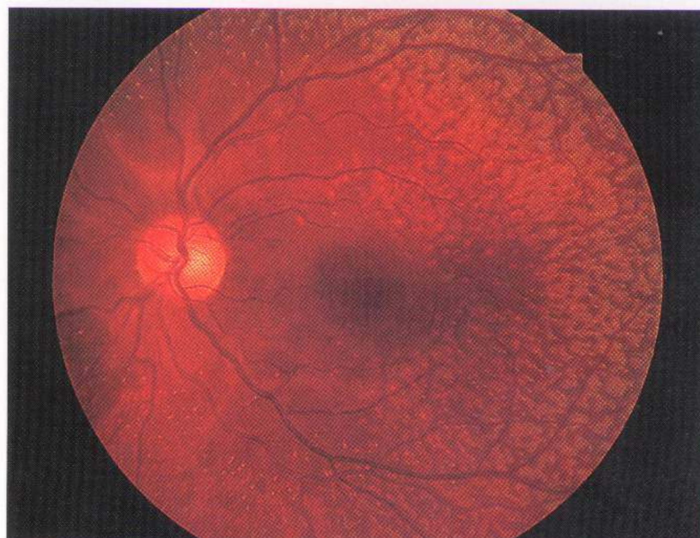


Fig. 15.50
Benign familial fleck retina

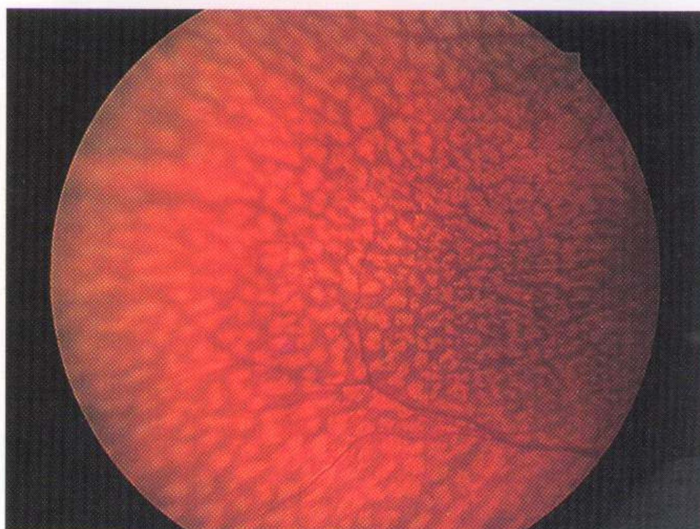


Fig. 15.51
Benign familial fleck retina

1. **Inheritance** is AR.
2. **Presentation** is with blindness at birth or within the first few years of life. Many affected children see best under bright illumination.
3. **Signs**
   - The pupillary light reflexes are absent or diminished.
   - The fundi may be initially normal despite very poor vision.
   - The most common findings are patches of peripheral chorioretinal atrophy and granularity.
   - Other findings include disc oedema, salt-and-pepper changes (Fig. 15.52), diffuse white spots, macular coloboma and bull's eye maculopathy.
   - Optic disc pallor and arteriolar attenuation develop concurrently with the retinal changes.
4. **Other ocular features**
   - Hypermetropia, keratoconus and keratoglobus.
   - Cataracts may develop by the second decade.
   - Nystagmus, roving eye movements and strabismus.
   - A characteristic feature is the oculodigital syndrome in which constant rubbing of the eyes by the child causes enophthalmos as a result of resorption of orbital fat (Fig. 15.53).
5. **ERG** is usually non-recordable even in early cases with normal fundi.
6. **Prognosis** is very poor.
7. **Systemic associations** include mental handicap, deafness, epilepsy, CNS and renal anomalies, skeletal malformations and endocrine dysfunction.

Congenital stationary night blindness

Normal fundus

1. **AD** congenital nyctalopia (Nougaret type) is characterized by a slightly impaired cone ERG and subnormal rod ERG.



Fig. 15.52
Leber congenital amaurosis (Courtesy of Wilmer Institute)



Fig. 15.53
Oculodigital syndrome (Courtesy of M. Szreter)

2. **AD** stationary nyctalopia without myopia (Riggs type) is characterized by a normal cone ERG.
3. **AR or XL** congenital nyctalopia with myopia (Schubert–Bornschein type).

Abnormal fundus

1. **Oguchi disease** is an AR condition characterized by a 2–12-hour delay in attaining normal dark-adapted rod thresholds. There is an accompanying change in fundus colour from golden-brown in the light-adapted state to a normal colour in the dark-adapted state (Mizuo phenomenon).
2. **Fundus albipunctatus** is an AR condition characterized by a multitude of tiny yellow-white spots at the posterior pole, sparing the fovea (Fig. 15.54) and extending to the periphery (Fig. 15.55). The retinal blood vessels, optic disc, peripheral fields and visual acuity remain normal. The ERG and EOG may be abnormal when tested

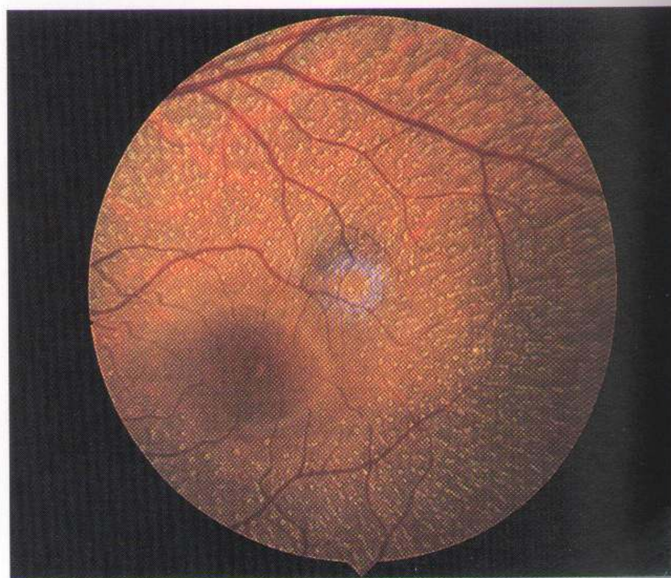


Fig. 15.54
Fundus albipunctatus

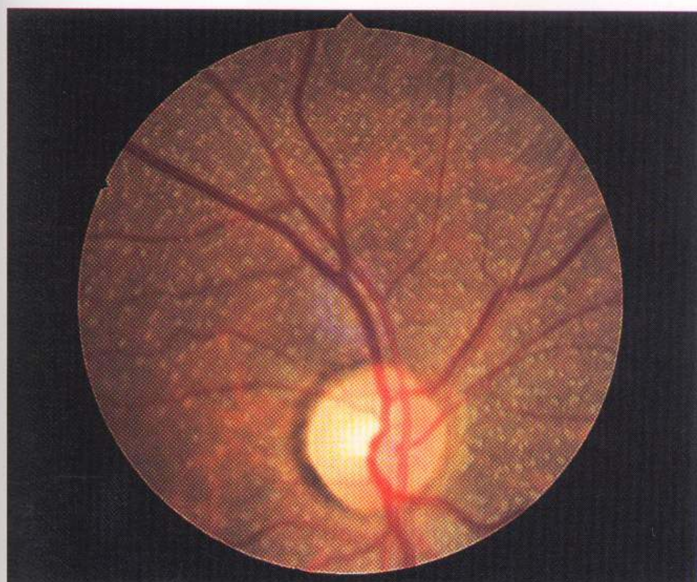


Fig. 15.55
Fundus albipunctatus

routinely but revert to normal on prolonged dark adaptation.

Congenital monochromatism

Complete rod monochromatism

1. **Inheritance** is AR.
2. **Signs**
   - Visual acuity is 6/60.
   - Macula usually appears normal but may be hypoplastic.
   - Congenital nystagmus and photophobia.
3. **ERG**. Photopic abnormal; scotopic may be subnormal; flicker fusion <30 Hz.
4. **CV** is totally absent; all colours appear as shades of grey.

Incomplete rod monochromatism

1. **Inheritance** is AR or XL.
2. **Signs**
   - Visual acuity is 6/12–6/24.
   - Macula is usually normal.
   - Nystagmus and photophobia may be present.
3. **ERG**. Photopic abnormal; scotopic normal.
4. **CV**. Some colour vision may be present.

Cone monochromatism

1. **Inheritance** is uncertain.
2. **Signs**
   - Visual acuity is 6/6–6/9.
   - Normal macula.
   - Nystagmus and photophobia are absent.
3. **ERG** is normal.
4. **CV** is totally absent.

Choroidal dystrophies

Choroideremia

Choroideremia is a very rare condition which only affects males.

1. **Inheritance** is XL recessive with the gene locus on Xq21. This has the following implications:
   - All daughters of affected fathers will be carriers.
   - Half of the sons of female carriers will develop the disease.
   - Half of the daughters of female carriers will also be carriers.
   - An affected male cannot transmit the gene to his sons.
2. **Female carriers** show mild, usually innocuous, patchy peripheral atrophy and mottling of the RPE (Fig. 15.56). However, visual acuity, peripheral fields and ERG are normal.
3. **Presentation** is in the first decade with nyctalopia.
4. **Signs** (in chronological order)
   - Mid-peripheral patches of choroidal and RPE atrophy (Fig. 15.57).
   - Diffuse atrophy of the choriocapillaris and RPE with preservation of the intermediate and large choroidal vessels (Fig. 15.58).
   - Atrophy of intermediate and large choroidal vessels rendering visible the underlying sclera (Fig. 15.59).

> *NB:* In contrast to primary retinal dystrophies, the fovea is spared until late (Fig. 15.60a) and the optic disc and retinal blood vessels remain relatively normal.

5. **ERG**. Scotopic ERG is non-recordable; photopic is severely subnormal.
6. **EOG** is subnormal.
7. **FA** of the intermediate stage of choroideremia shows filling of the retinal and large choroidal vessels but not of the choriocapillaris. There is also hypofluorescence

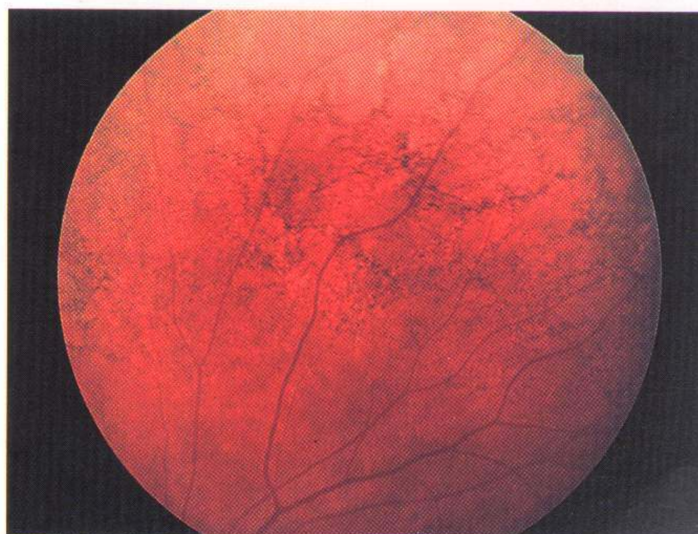


Fig. 15.56
Peripheral changes in a carrier of choroideremia

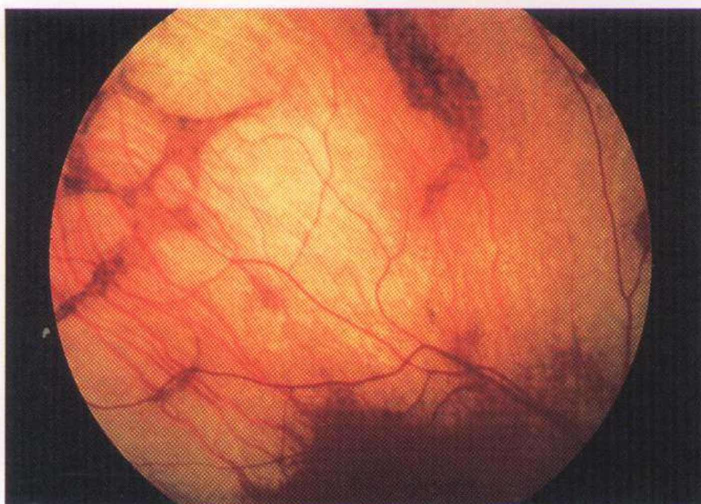


Fig. 15.57
Mid-peripheral changes in choroideremia (Courtesy of K. Jordan)

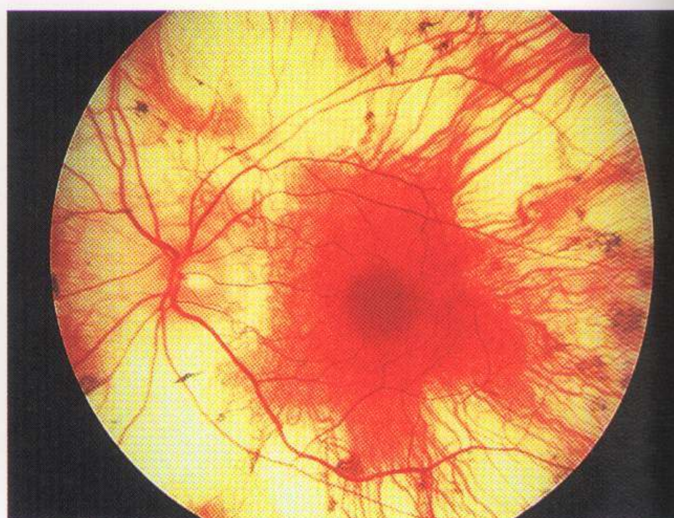


Fig. 15.59
Advanced choroideremia (Courtesy of K. Nischal)

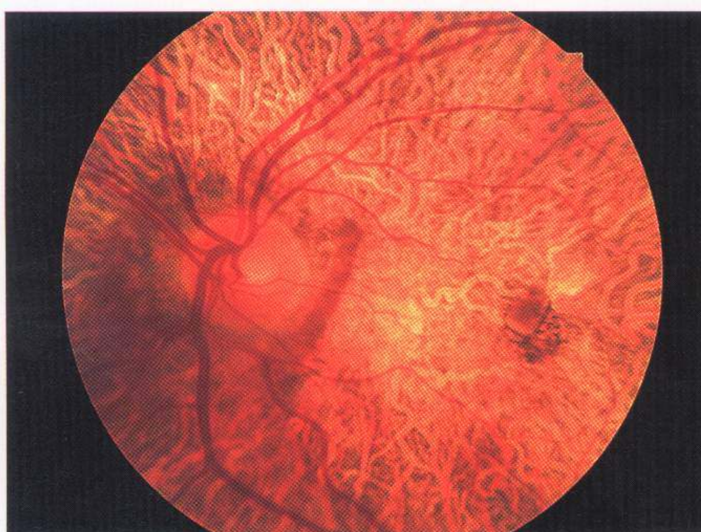


Fig. 15.58
Choroideremia with preservation of intermediate and large choroidal vessels

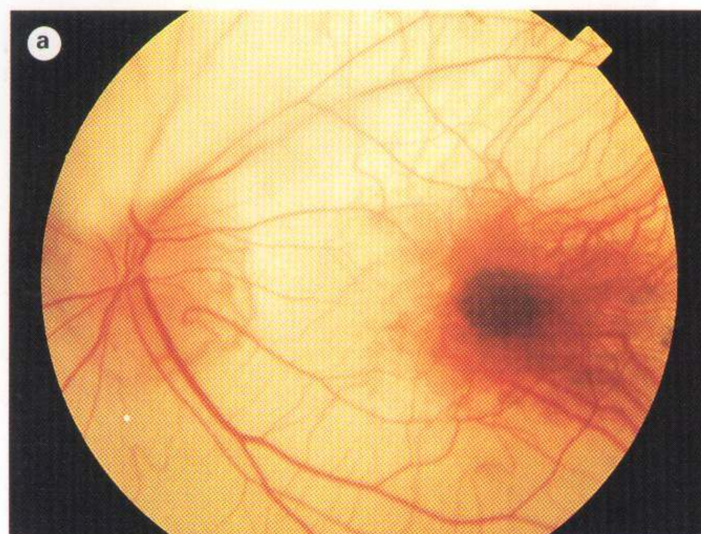
corresponding to the intact fovea and a surrounding area of hyperfluorescence due to a window defect (Fig. 15.60b).

8. **Prognosis** is very poor; although most patients retain useful vision until the sixth decade, very severe visual loss occurs thereafter.

Gyrate atrophy

Gyrate atrophy of the choroid and retina is caused by mutations of the gene encoding the main ornithine degradation enzyme, ornithine keto-acid aminotransferase. Deficiency of the enzyme leads to elevated ornithine levels in the plasma, urine, CSF and aqueous humour.

1. **Inheritance** is AR.
2. **Presentation** is in the second decade with axial myopia and nyctalopia.
3. **Signs** (in chronological order)
   - Peripheral patches of chorioretinal atrophy (Fig. 15.61) and vitreous degeneration.



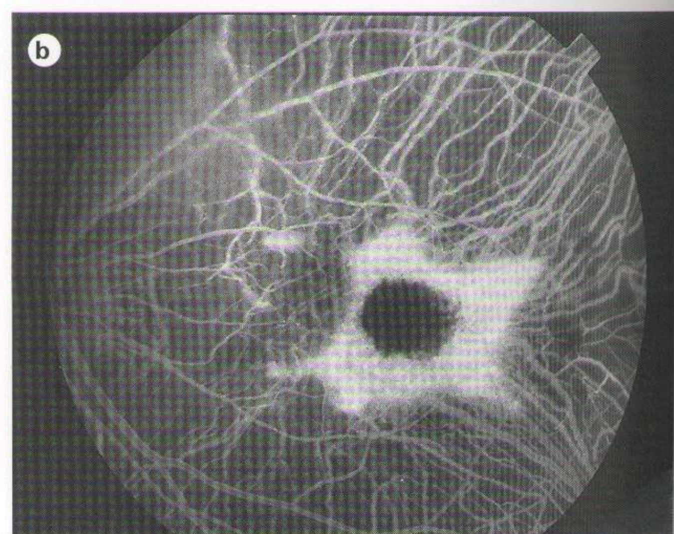


Fig. 15.60
(a) End-stage choroideremia; **(b)** FA showing diffuse loss of the choriocapillaris with preservation of the fovea (Courtesy of S. Milewski)

- Confluence of lesions forming a scalloped posterior border (Fig. 15.62).
- Gradual peripheral and central spread, sparing the fovea until late (Figs 15.63 and 15.64a).

> *NB:* In contrast to choroideremia there is extreme attenuation of retinal blood vessels.

4. **ERG** is abnormal and later extinguished.
5. **EOG** is subnormal in late disease.
6. **FA** shows the sharp contrast between normal and atrophic areas (Fig. 15.64b).
7. **Prognosis** is poor with legal blindness occurring in the fourth to sixth decades from geographic atrophy, although vision may fail earlier due to cataract, CMO or epiretinal membrane formation.
8. **Treatment**. There are two clinically different subtypes of gyrate atrophy based on response to pyridoxine (vitamin B_6), which may normalize plasma and urinary ornithine levels. Patients responsive to vitamin B_6 generally have a less severe and more slowly progressive clinical course than those who

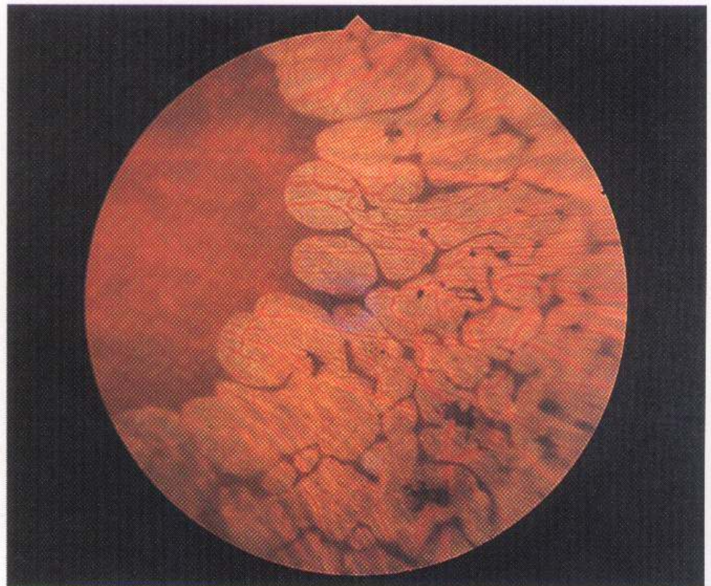


Fig. 15.62
Coalescent gyrate atrophy

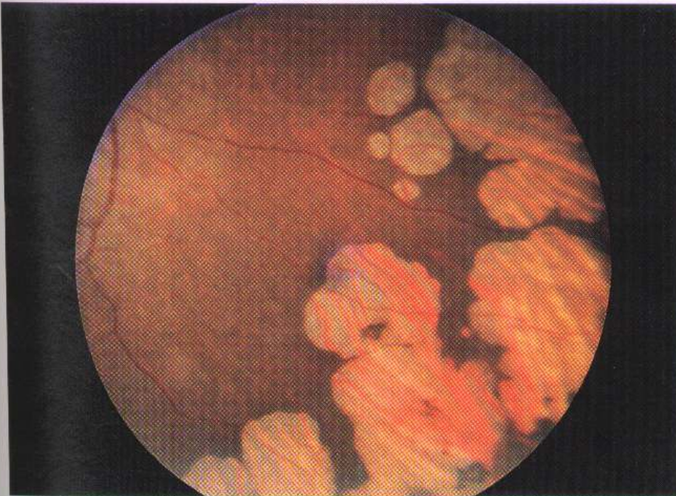


Fig. 15.61
Peripheral patches of gyrate atrophy

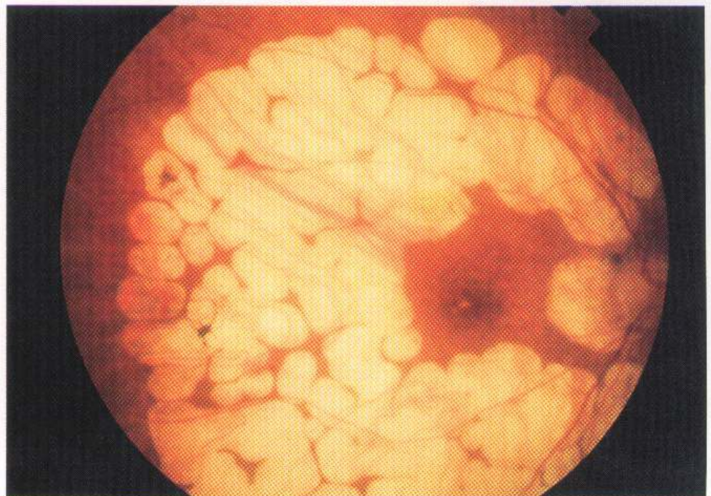
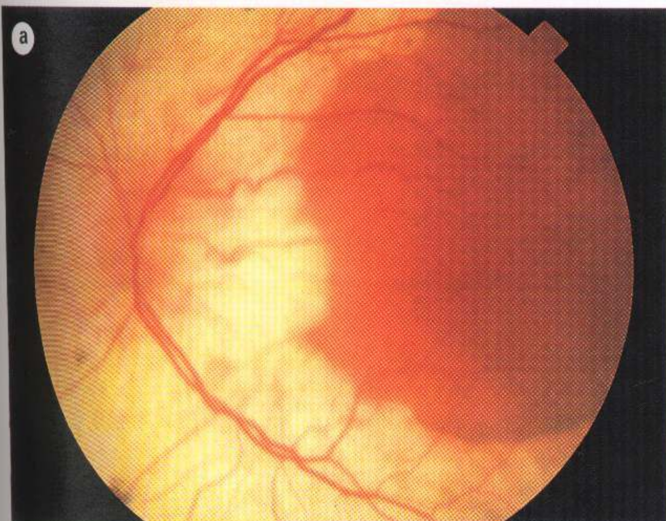


Fig. 15.63
Advanced gyrate atrophy



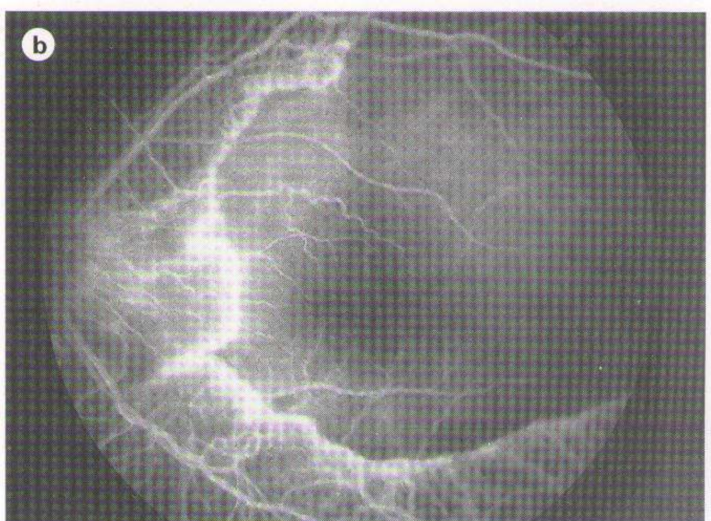


Fig. 15.64
(a) Gyrate atrophy; (**b**) FA showing sharp contrast between normal and atrophic areas (Courtesy of S. Milewski)

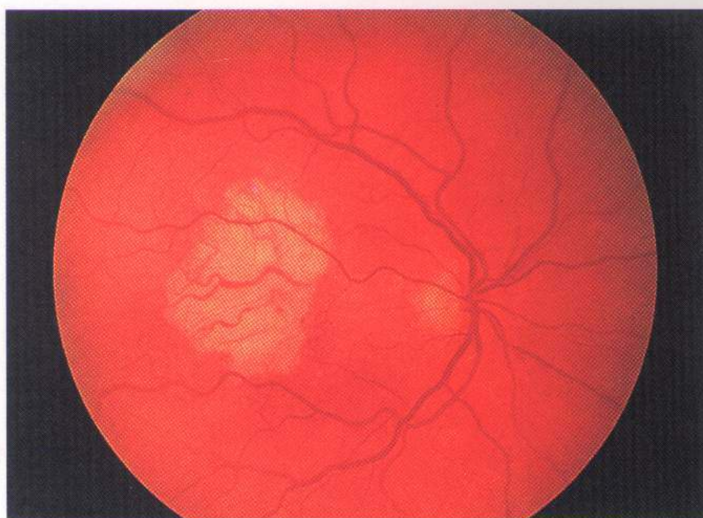


Fig. 15.65
Central areolar choroidal dystrophy

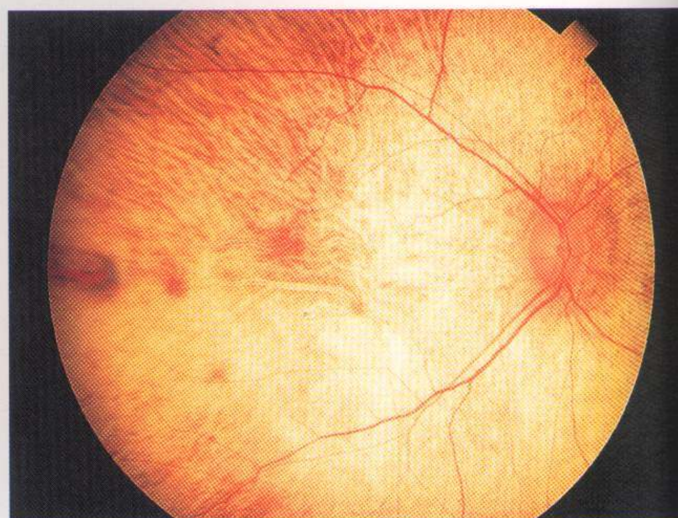


Fig. 15.66
Diffuse choroidal atrophy (Courtesy of S. Milewski)

are not. Reduction in ornithine levels with an arginine-restricted diet is also beneficial in slowing progression.

Central areolar choroidal dystrophy

1. **Inheritance** is AD with the gene locus on 17p.
2. **Presentation** is in the third to fourth decades with gradual, bilateral impairment of central vision.
3. **Signs** (in chronological order)
   - Non-specific foveal granularity.
   - Circumscribed RPE atrophy and loss of the choriocapillaris at the macula.
   - Slowly expanding geographic atrophy within which the larger choroidal vessels are prominent (Fig. 15.65).
4. **ERG** is normal.
5. **EOG** is normal.
6. **Prognosis** is poor with severe visual loss occurring by the sixth to seventh decades.

Diffuse choroidal atrophy

1. **Inheritance** is AD.
2. **Presentation** is in the fourth to fifth decades with impairment of central vision or nyctalopia.
3. **Signs** (in chronological order)
   - Parapapillary and pericentral atrophy of the RPE and choriocapillaris.
   - Gradual enlargement until the entire fundus is affected.
   - Atrophy of most of the larger choroidal vessels with scleral visibility (Fig. 15.66).
   - The retinal vessels may be normal or slightly constricted.
4. **ERG** is subnormal.
5. **Prognosis** is poor because of early macular involvement.

Helicoidal parapapillary chorioretinal degeneration

1. **Inheritance** is AD.
2. **Presentation** is in childhood.
3. **Signs**
   - Bilateral, slowly-enlarging, tongue-like, well-defined strips of chorioretinal atrophy radiating from the optic nerve head (Fig. 15.67).
   - Separate, peripheral, circular lesions may be present.
4. **ERG** ranges from normal to severely abnormal.
5. **Prognosis** is variable as severe disease may be seen in the young and mild disease in the elderly.

Pigmented paravenous retinochoroidal atrophy

Pigmented paravenous retinochoroidal atrophy is a rare condition, usually discovered incidentally in young men.

1. **Inheritance**. No distinctive pattern has been established although AD, AR, XL and even YL transmissions have been proposed.
2. **Signs**
   - Bilateral, bone corpuscular pigment accumulation along major retinal veins.
   - Adjacent, sharply outlined zones of chorioretinal atrophy which may surround the disc (Fig. 15.68).
3. **ERG** is usually normal.
4. **Prognosis** is excellent because macular involvement is rare.

Vitreoretinopathies

Congenital retinoschisis

Congenital retinoschisis is characterized by bilateral maculopathy, associated with peripheral retinoschisis in 50% of patients. The basic defect is in the Müller cells, causing splitting of the retinal nerve fibre layer from the rest of the sensory retina. This differs from acquired retinoschisis in which splitting occurs at the outer plexiform layer.

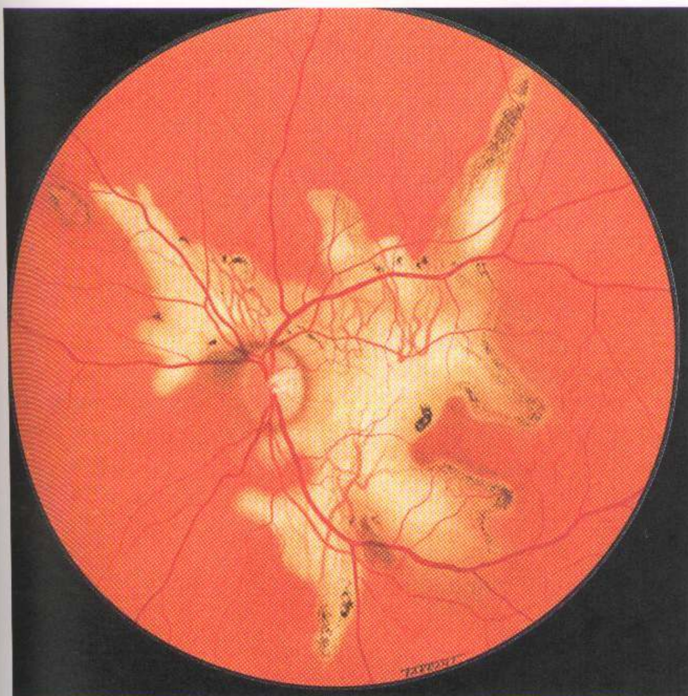


Fig. 15.67
Helicoid chorioretinal degeneration

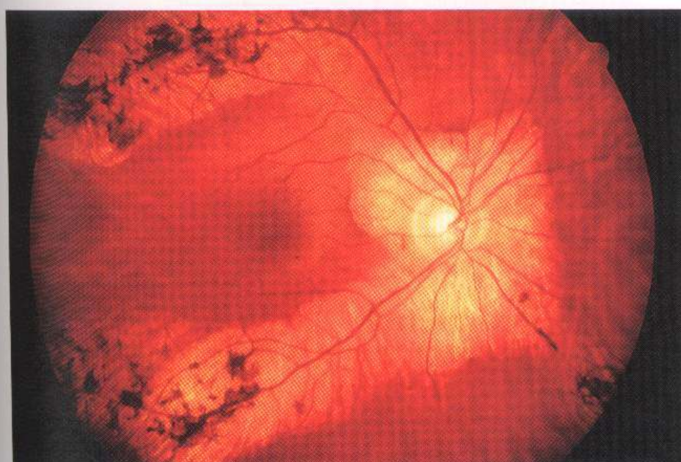


Fig. 15.68
Pigmented paravenous chorioretinal atrophy (Courtesy of C. Barry)

1. **Inheritance** is XL with the gene designated RS1.
2. **Presentation** is between the ages of 5 and 10 years with reading difficulties due to maculopathy. Less frequently the disease presents in infancy with squint or nystagmus associated with advanced peripheral retinoschisis often with vitreous haemorrhage.
3. **Signs**
   a. *Foveal schisis* is characterized by tiny cystoid spaces with a 'bicycle-wheel' pattern of radial striae (Fig. 15.69) more apparent when examined under red-free light. Over time the radial folds become less evident, leaving a blunted foveal reflex (*see* Fig. 15.73a).
   b. *Peripheral schisis* predominantly involves the inferotemporal quadrant, does not extend but may undergo the following secondary changes:

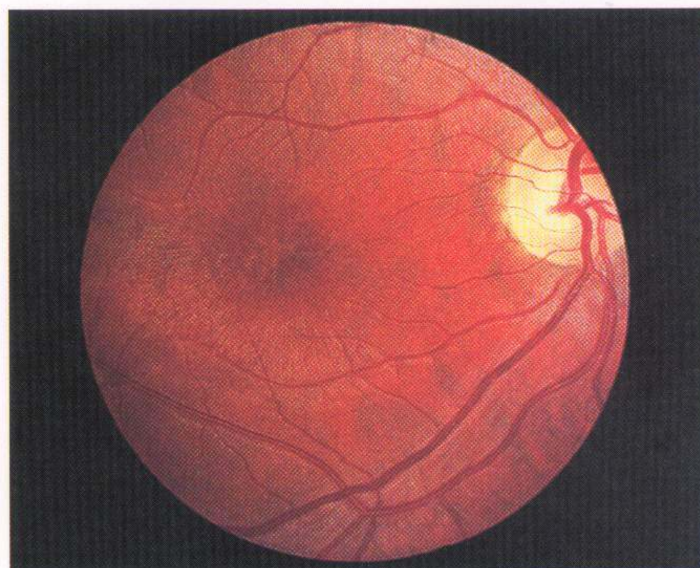


Fig. 15.69
'Bicycle wheel-like' maculopathy in congenital retinoschisis (Courtesy of P. Morse)

   - The inner layer, which consists only of the internal limiting membrane and the retinal nerve fibre layer, may develop oval defects (Figs 15.70 and 15.71).
   - In extreme cases, the defects coalesce, leaving only retinal blood vessels floating in the vitreous ('vitreous veils').

   c. *Other signs* include perivascular sheathing, a golden glistening of the peripheral retina, nasal dragging of retinal vessels, retinal flecks, subretinal exudates and neovascularization.
4. **Complications** include vitreous and intra-schisis haemorrhage, and retinal detachment.
5. **ERG** is normal in eyes with isolated maculopathy. Eyes with peripheral schisis show a characteristic selective

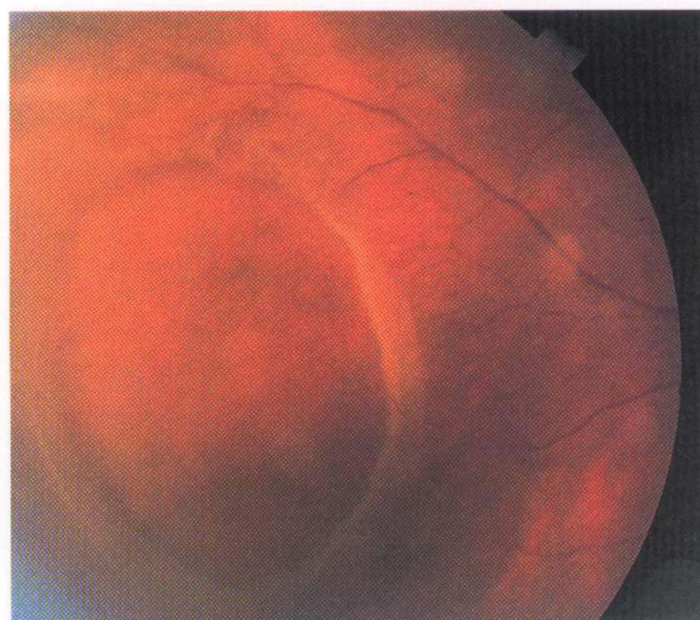


Fig. 15.70
Defect in the inner leaf of congenital retinoschisis

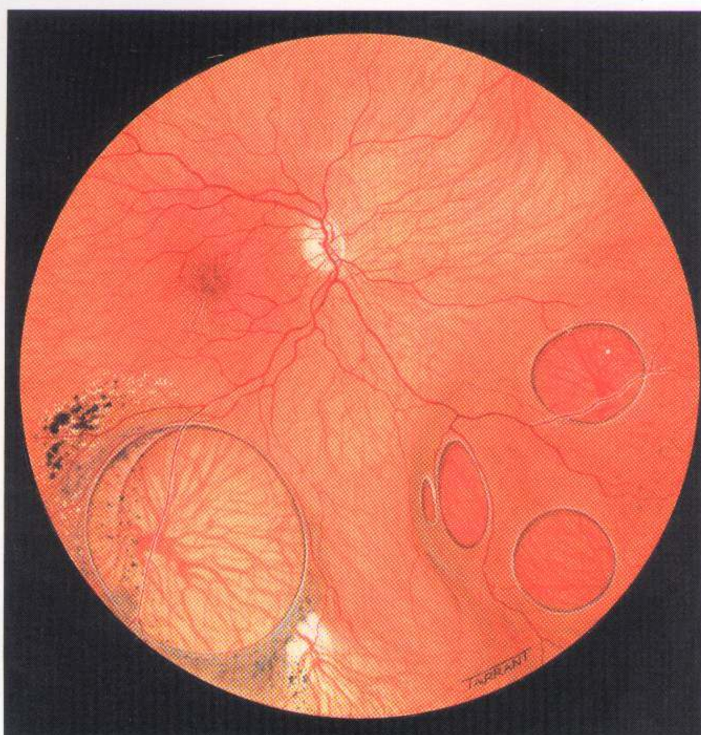


Fig. 15.71
Large defects in the inner leaf of congenital retinoschisis

decrease in b-wave amplitude as compared with a-wave amplitude on scotopic and photopic testing (Fig. 15.72).

6. **EOG** is normal in eyes with isolated maculopathy but subnormal in eyes with advanced peripheral lesions.
7. **CV** shows tritan defect.
8. **FA** of maculopathy may show mild window defects but no leakage (Fig. 15.73b).
9. **Visual fields** in eyes with peripheral schisis show corresponding absolute defects.
10. **Prognosis** is poor due to progressive maculopathy. Visual acuity deteriorates during the first two decades and may then remain stable until the fifth or sixth decade when it further deteriorates. Patients with peripheral schisis may have sudden visual loss at any time due to haemorrhage or retinal detachment.

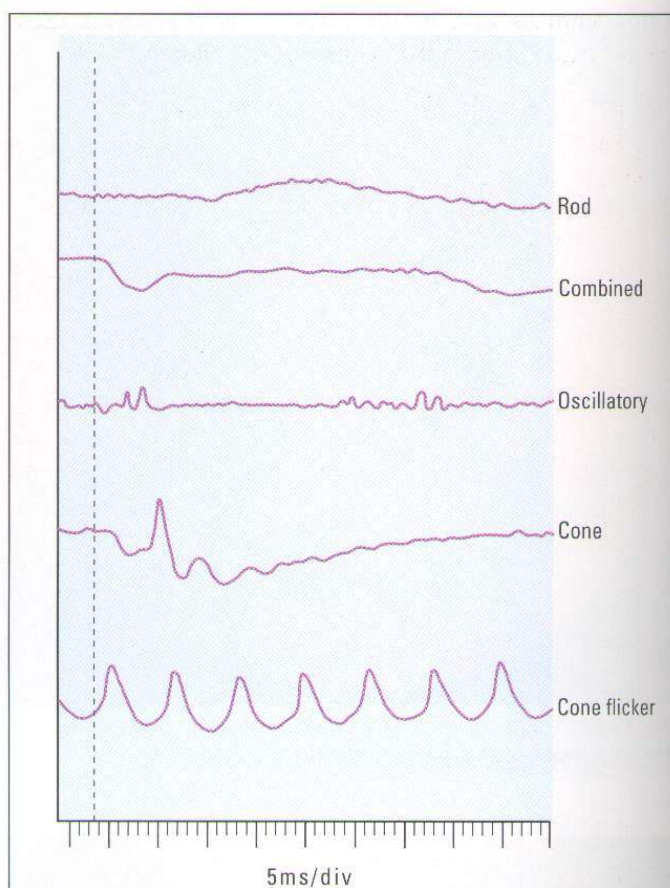
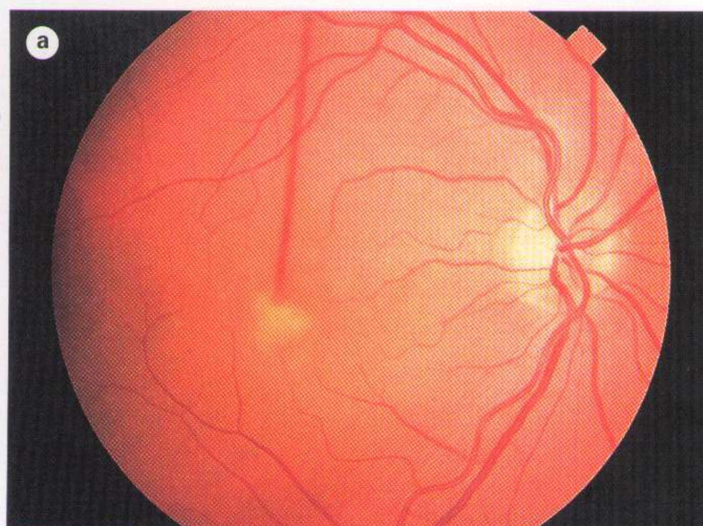


Fig. 15.72
Electroretinogram in congenital retinoschisis *(see text)*

Stickler syndrome

Stickler syndrome (hereditary arthro-ophthalmopathy) is a disorder of collagen connective tissue, resulting in abnormal vitreous, myopia, and a variable degree of orofacial abnor-



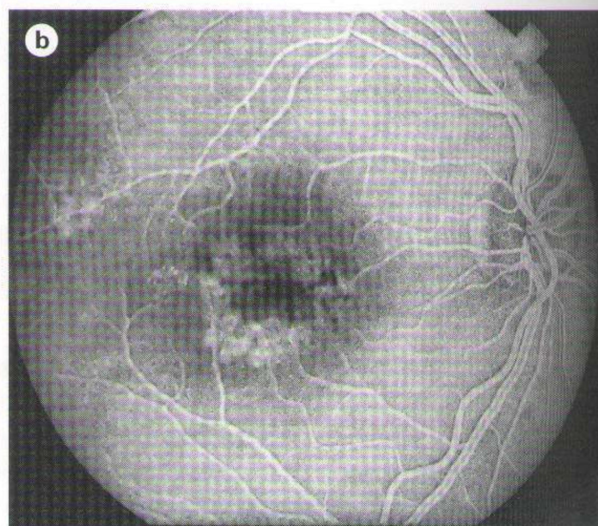


Fig. 15.73
(**a**) Late-stage maculopathy in congenital retinoschisis; (**b**) FA showing window defects

mality, deafness and arthropathy. It is the commonest inherited cause of retinal detachment in children.

1. **Inheritance** is AD with complete penetrance but variable expressivity.
2. **Signs**
   - An optically empty vitreous cavity due to liquefaction and syneresis.
   - Circumferential, equatorial, translucent membranes extending a short way into the vitreous cavity (Fig. 15.74).
   - Radial lattice-like degeneration associated with RPE hyperplasia, vascular sheathing and sclerosis (Fig. 15.75).
3. **Complications**. Retinal detachment, often bilateral, develops in approximately 30% of cases due to multiple or giant tears. Because the prognosis is poor, patients should be examined regularly and retinal breaks treated prophylactically.

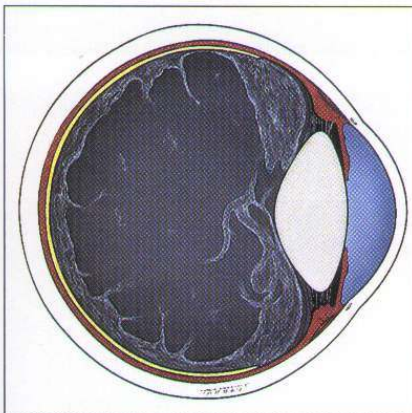


Fig. 15.74
Empty vitreous in Stickler syndrome

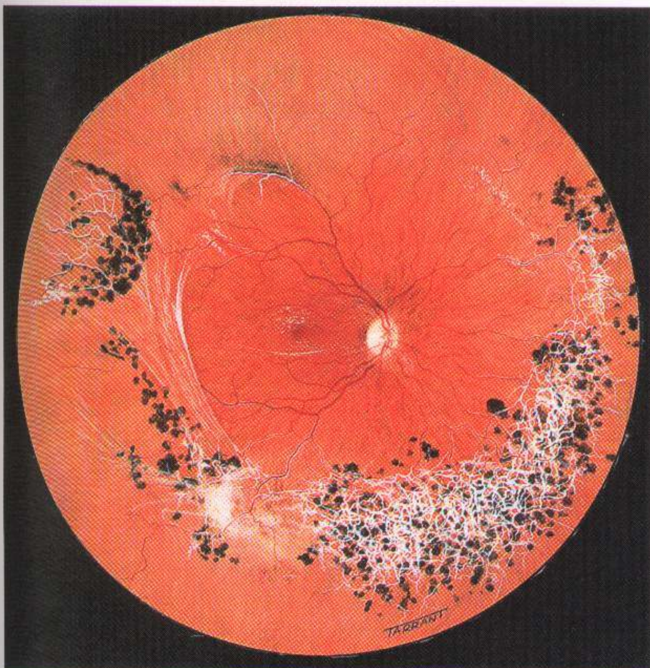


Fig. 15.75
Radial lattice degeneration and pigmentary changes in Stickler syndrome

4. **Associations**
   a. *Congenital high myopia* is very common.
   b. *Presenile cataract*, in 50% of cases, is characterized by peripheral cortical wedge-shaped opacities, which are frequently non-progressive.
   c. *Ectopia lentis* in about 10%.
   d. *Glaucoma* in 10% of cases due to an angle anomaly similar to that seen in Marfan syndrome.
5. **Systemic features**
   a. *Facial* anomalies include a flattened nasal bridge and maxillary hypoplasia.
   b. *Skeletal* involvement includes a marfanoid habitus, arthropathy and joint hyperextensibility.
   c. *Robin sequence* is characterized by micrognathia, glossoptosis, cleft soft palate and high-arched palate.
   d. *Other* features include deafness and mitral valve prolapse.
6. **Differential diagnosis**. Wagner syndrome has ocular similarities with Stickler. However, it is not associated with systemic disease, myopia is mild and retinal detachment is uncommon.

Favre–Goldmann syndrome

Favre–Goldmann syndrome has features of retinoschisis and pigmentary retinopathy.

1. **Inheritance** is AR.
2. **Presentation** is in childhood with nyctalopia.
3. **Signs**
   - Vitreous shows syneresis but the cavity is not optically 'empty'.
   - Retinal lesions are similar to congenital retinoschisis, although the macular findings are more subtle.
   - Pigmentary retinopathy (similar to RP) and white, dendritiform, arborescent peripheral retinal vessels (Fig. 15.76).
4. **ERG** is subnormal.
5. **Prognosis** is poor.

Familial exudative vitreoretinopathy

Familial exudative vitreoretinopathy (Criswick–Schepens syndrome) is a slowly progressive condition characterized by avascularity of the temporal retinal periphery, similar to retinopathy of prematurity, but not associated with low birth weight and prematurity.

1. **Inheritance** is AD and rarely XL recessive with high penetrance and variable expressivity.
2. **Presentation** is in late childhood.
3. **Signs** (in chronological order)
   - Vitreous degeneration and peripheral vitreoretinal attachments associated with areas of 'white without pressure'.
   - Peripheral vascular tortuosity, telangiectasia (Fig. 15.77), neovascularization, haemorrhages and subretinal exudates.

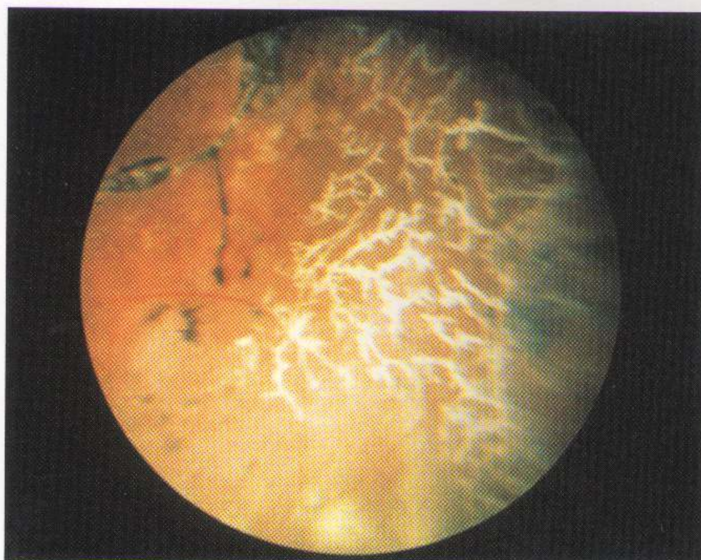


Fig. 15.76
Peripheral dendritiform lesions in Favre–Goldmann syndrome (Courtesy of Moorfields Eye Hospital)

- Fibrovascular proliferation (Fig. 15.78) and vitreoretinal traction resulting in ridge formation (Fig. 15.79), vascular straightening, localized retinal detachment and temporal dragging of the macula (Fig. 15.80).
- Extensive tractional retinal detachment, massive subretinal exudation, band keratopathy, cataract and glaucoma.

4. **ERG** is normal.
5. **FA** shows peripheral retinal non-perfusion and highlights straightening of blood vessels (Fig. 15.81).
6. **Prognosis** is poor although in some cases peripheral retinal laser photocoagulation or cryotherapy may be beneficial. Vitreoretinal surgery for retinal detachment is difficult but may be successful in selected cases.

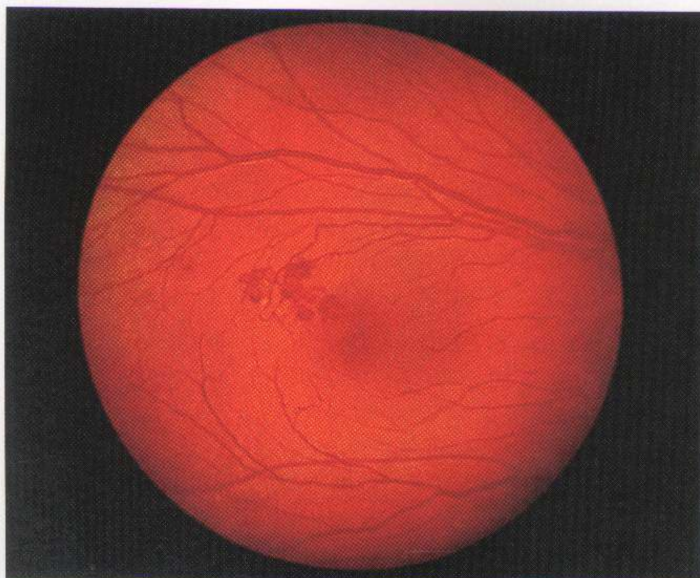


Fig. 15.77
Telangiectasia in familial exudative vitreoretinopathy

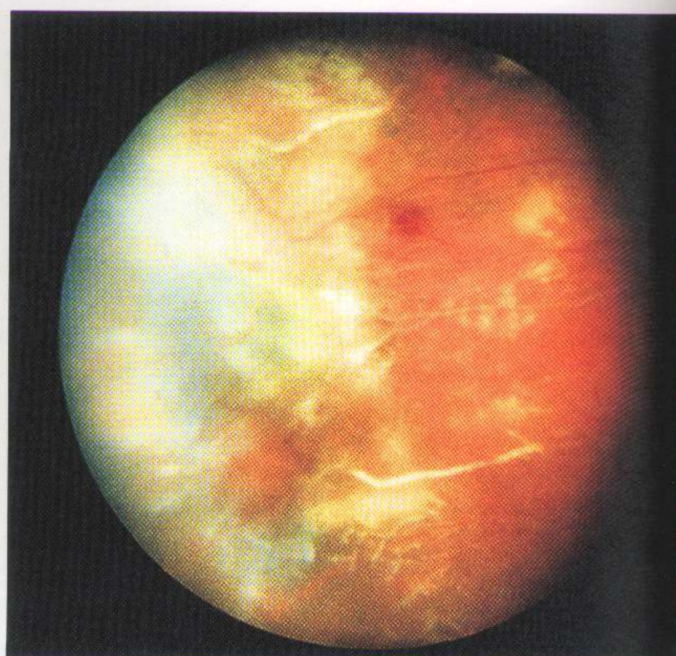


Fig. 15.78
Fibrovascular proliferation in familial exudative vitreoretinopathy

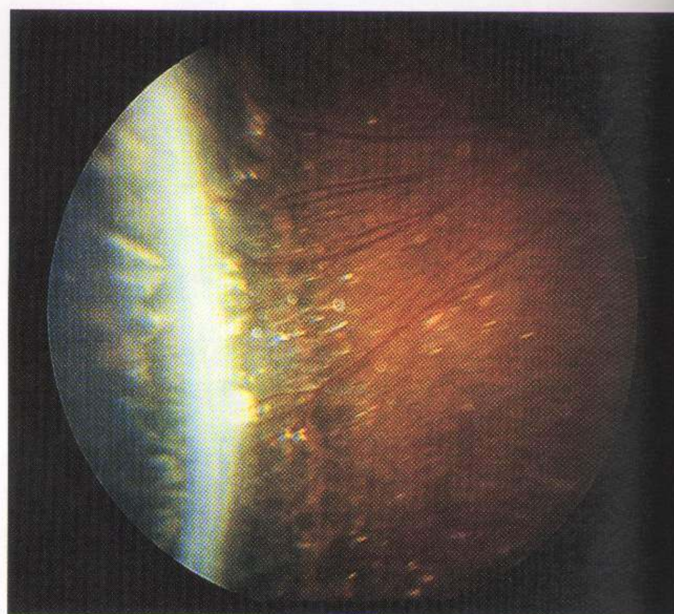


Fig. 15.79
Fibrovascular ridge in familial exudative vitreoretinopathy

Erosive vitreoretinopathy

1. **Inheritance** is AD.
2. **Presentation** is in early life.
3. **Signs**
   - Vitreous syneresis and multiple foci of vitreoretinal traction.
   - Thinning of the RPE and progressive choroidal atrophy which may eventually involve the macula and resemble choroideremia.
4. **Complications**. Retinal detachment in 70%, often bilateral and caused by giant tears.

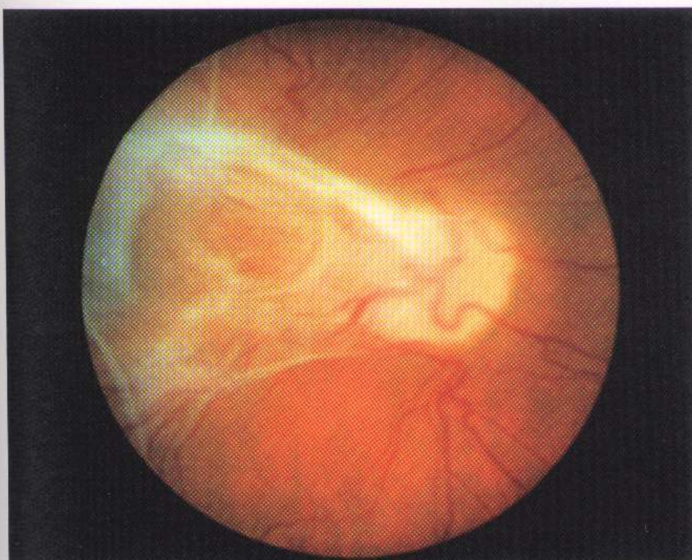


Fig. 15.80
'Dragging' of the macula in familial exudative vitreoretinopathy

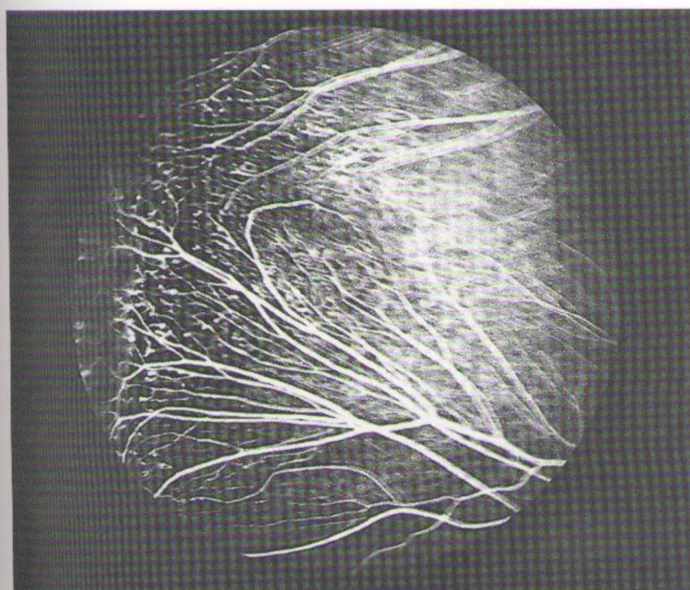


Fig. 15.81
FA in familial exudative vitreoretinopathy showing abrupt termination of peripheral retinal vasculature

5. **ERG** is subnormal.
6. **Prognosis** is guarded because retinal detachment may be difficult to treat.

Dominant neovascular inflammatory vitreoretinopathy

1. **Inheritance** is AD.
2. **Presentation** is in the second to third decades with vitreous floaters.
3. **Signs**
   - Uveitis.
   - Pigmentary retinal degeneration.
   - Peripheral vascular closure and neovascularization.
4. **Complications** include vitreous haemorrhage, tractional retinal detachment and cystoid macular oedema.
5. **ERG** shows selective loss of b-wave amplitude.
6. **Prognosis** is guarded. Peripheral retinal photocoagulation and vitreous surgery may be required to preserve vision.

Dominant vitreoretinochoroidopathy

1. **Inheritance** is AD.
2. **Presentation** is in adult life if symptomatic, but frequently the condition is discovered by chance.
3. **Signs**
   - An encircling band of pigmentary disturbance between the ora serrata and equator with a sharply defined posterior border.
   - Within the band there is arteriolar attenuation, neovascularization, punctate white opacities and later chorioretinal atrophy.
4. **Complications**, which are uncommon, include cystoid macular oedema and occasionally vitreous haemorrhage.
5. **ERG** is subnormal.
6. **Prognosis** is good.

Albinism

Albinism is a genetically determined heterogeneous group of disorders involving hypopigmentation of the eyes and/or skin, due to a deficiency of tyrosinase, which mediates the conversion of tyrosine to melanin. The two types are (a) *oculocutaneous* and (b) *ocular*. The former may be tyrosinase-negative or tyrosinase-positive and is inherited as AR, while the latter is commonly XL.

Oculocutaneous albinism

Tyrosinase-negative

These albinos are incapable of synthesizing melanin and have blond hair and very pale skin (Fig. 15.82).

1. **Iris** is diaphanous and translucent (Fig. 15.83), giving rise to a 'pink-eyed' appearance.
2. **Fundus** (Fig. 15.84).
   - Lack of pigment with conspicuously large choroidal vessels.
   - Hypoplasia of vessels forming the perimacular arcades.
   - Foveal and optic nerve hypoplasia may be present.
3. **Refractive errors** are common and visual acuity is usually <6/60.
4. **Nystagmus** is usually pendular and horizontal, and increases on bright illumination. Its severity may lessen with age.

5. **The chiasm** has a decreased number of uncrossed nerve fibres. Abnormal visual pathways also exist from the lateral geniculate body to the occipital cortex.

Tyrosinase-positive

These albinos can synthesize variable amounts of melanin and vary in complexion from very fair to almost normal.

1. **Iris** may be blue or dark-brown with variable translucency (Fig. 15.85).
2. **Fundus** shows variable hypopigmentation (Fig. 15.86).
3. **Visual acuity** is usually impaired due to foveal hypopiasia.
4. **Associated syndromes**
   a. *Chediak–Higashi syndrome* is associated with white cell abnormalities resulting in recurrent pyogenic infections and an early demise.



Fig. 15.82
Blond hair and pink-eyed appearance in tyrosinase-negative oculocutaneous albinism

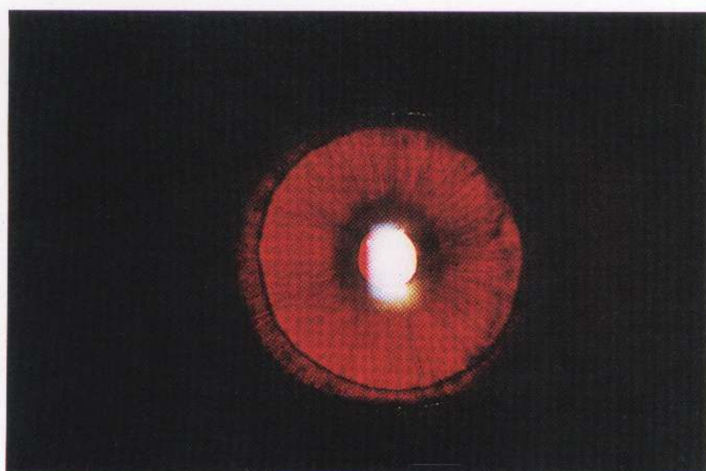


Fig. 15.83
Iris transillumination in tyrosinase-negative oculocutaneous albinism

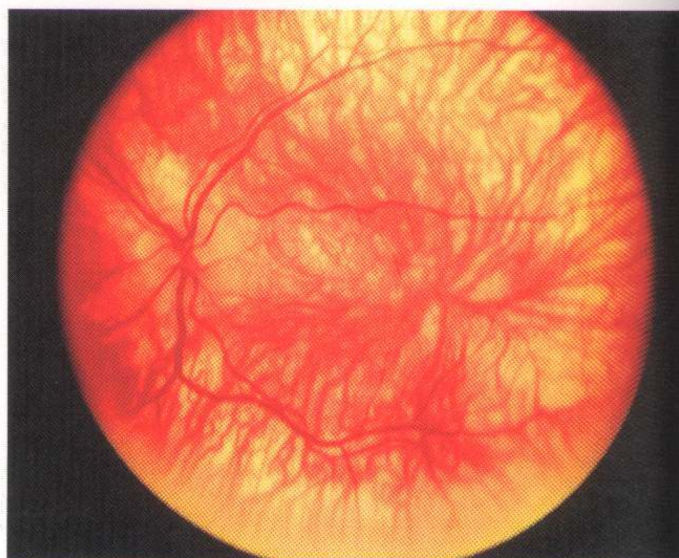


Fig. 15.84
Severe fundus hypopigmentation in tyrosinase-negative oculocutaneous albinism (Courtesy of K. Nischal)

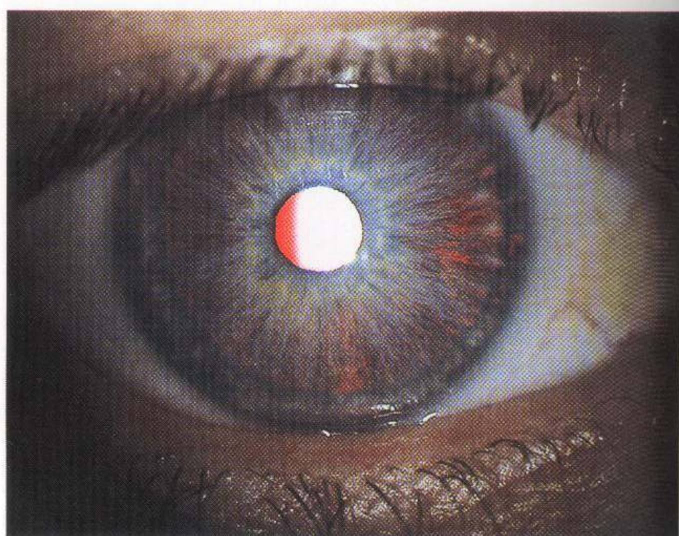


Fig. 15.85
Partial iris transillumination in tyrosinase-positive albinism

   b. *Hermansky–Pudlak syndrome* is a lysosomal storage disease of the reticuloendothelial system characterized by easy bruising due to platelet dysfunction.

Ocular albinism

The eyes are predominantly affected, with less evident skin and hair involvement.

1. **Inheritance** is XL or, less commonly, AR.
2. **Female carriers** are asymptomatic and have normal vision, although they may show partial iris translucency, macular stippling and scattered areas of depigmentation and granularity in the mid-periphery (Fig. 15.87).
3. **Affected males** manifest hypopigmented irides and fundi.

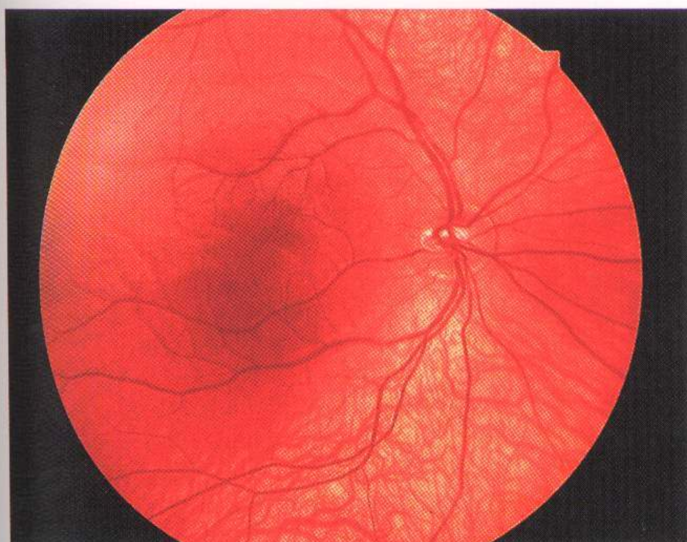


Fig. 15.86
Mild fundus hypopigmentation in tyrosinase-positive albinism

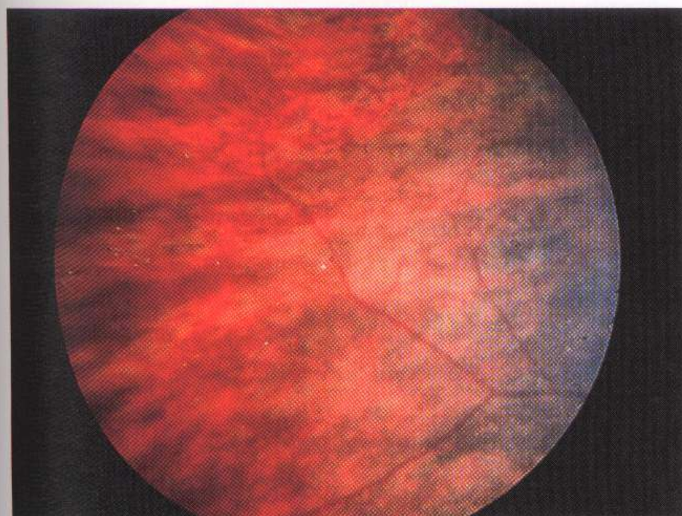


Fig. 15.87
Peripheral fundus changes in a female carrier of X-linked ocular albinism

Cherry-red spot at macula

The cherry-red spot at the macula is a clinical sign seen in the context of thickening and loss of transparency of the retina at the posterior pole. The foveola, being the thinnest part of the retina and devoid of ganglion cells, retains relative transparency, due to which the colour of the choroid shines through. This striking retinal lesion, commonly seen in occlusion of the central retinal artery, is additionally a feature of a rare group of inherited metabolic diseases which comprise the sphingolipidoses. These diseases are characterized by the progressive intracellular storage of excessive quantities of certain glycolipids and phospholipids in various tissues of the body, including the retina. The lipids are stored in the ganglion cell layer of the retina, giving the retina a white appearance. As ganglion cells are absent at the foveola, this area retains relative transparency and contrasts with the surrounding opaque retina (Fig. 15.88). With the passage of time the ganglion cells die and the spot becomes less evident. The late stage of the disease is characterized by atrophy of the retinal nerve fibre layer and consecutive optic atrophy. Systemic associations are as follows:



Fig. 15.88
Cherry-red spot at the macula in Tay–Sachs disease

1. **Tay–Sachs disease** (Gm2 gangliosidosis type 1), also called infantile amaurotic familial idiocy, is an autosomal recessive disease with an onset during the first year of life, usually ending in death before the age of 2 years. It typically affects European Jews and is characterized by progressive neurological disease and eventual blindness. A cherry-red spot is present in about 90% of cases.
2. **Niemann–Pick disease** is divided on a clinical and chemical basis into the following four groups:
   a. *Group A* with severe early CNS deterioration.
   b. *Group B* with normal CNS function.
   c. *Group C* with moderate CNS involvement and a slow course.
   d. *Group D* with a late onset and eventual severe CNS involvement.

   The incidence of a cherry-red spot is lower than in Tay–Sachs disease.
3. **Sandhoff disease** (Gm2 gangliosidosis type 2) is almost identical to Tay–Sachs disease.
4. **Generalized gangliosidosis** (Gm1 gangliosidosis type 1) is characterized by hypoactivity, oedema of the face and extremities, and skeletal anomalies from birth.
5. **Sialidosis types 1 and 2** (cherry-red spot myoclonus syndrome) are characterized by myoclonic jerks, pain in the limbs and unsteadiness. A cherry-red spot may be the initial finding.